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Division of Research Resources.

Annual Report.
July 1, 1975-June 30, 1976

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ANNUAL REPORT of program activities

FISCAL YEAR 1976
(July 1, 1975-June 30, 1976)

DIVISION OF RESEARCH RESOURCES

National Institutes of Health
Bethesda, Maryland 20014

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

Report of the Division Director

During Fiscal Year 1976, there has been a major and successful management effort to collectively muster and utilize the internal resources of the Division to meet the charge of the Director, NIH to engage in a study related --

> ". . . to the administrative structure of DRR and how this might be modified to better utilize management resources and assure coordination of programs."

A reorganization plan which was the result of studies conducted by DRR program and administrative staff was developed. It proposed improvements that would achieve better utilization of personnel, greater cohesion among the Division's programs, and enhanced effectiveness in realizing the Division's contemporary primary goal and basic objective:

- To identify and meet the research resource needs and opportunities of the NIH
- To conceive, create, develop, and assure the availability of those resources that are essential for the effective conduct of biomedical research.

The internal reorganization of the Division is based on the establishment and development of five integrative Division-wide functional systems that will enhance the unique strengths of our five highly differentiated programs, e.g., Animal Resources Program, Biotechnology Resources Program, Minority Biomedical Support Program, Biomedical Research Support Program (formerly General Research Support), General Clinical Research Centers Program.

These systems are Program Direction, Scientific and Technical Merit Review, Grants and Contracts Management, Integrated Information Management, and Scientific and Health Communications.

The five Program Directors and the five heads of each system constitute a Divisional Resource Directorate to assure that the programs and the functional systems are well formulated, understood, and executed to meet the Division's contemporary goal and objective. Areas of major emphasis to be addressed by the Resource Directorate are Division-level program planning, administration, and evaluation; and policy formulation and interpretation.

The strength of this mixed mode organizational concept of five differentiated programs and five integrative functional systems lies in its capability to sense and serve the changing research resource needs of the nationwide biomedical research community and the NIH.

With the official acceptance and implementation of plan by the Director, NIH in October 1975, the Resource Directorate has turned its collective

attention to the identification, prioritization, and establishment of even more effective processes for dealing with two broad areas:

Management Action Issues

- Development of a Five-Year Plan to include specific objectives, steps to reach those objectives, including the development of new programs and/or modification of existing programs.

- Development of a process to followup DRR/Institute Interfacing with tangible working agreements between DRR programs and various Institute components.

- The identification of a process to provide complete research highlight information from programs. The availability of this information would be geared to specific management/administrative milestones during the years.

Management Development Objectives

- Better problem-solving strategies and decision-making techniques.

- Improved decision-making consistent with role change in organization.

- Develop capability for non-hierarchical, functional operations.

- Evoking more points of view and risk taking.

With the Divisional internal realignment of resources essentially completed, we are focusing our attention on program development through the preparation of a Divisional Five-Year Plan that is proactive to NIH and grantee institutional needs. We seek to produce a plan that will lead and shape the budgetary allocation process rather than a plan dictated by the budgetary mechanics of the current "Forward Plans."

Thus, we look forward to the challenges and opportunities we anticipate from the report of the Scientific Mission Study currently being conducted by a distinguished outside panel of 15 specialists through a coordination contract with Bolt Beranek and Newman, Inc. of Boston, Massachusetts.

REPORT OF THE DEPUTY DIRECTOR

Dr. James F. O'Donnell

Report of the Deputy Director

A significant portion of the Deputy Director's efforts during Fiscal Year 1976 was directed to the establishment and development of a Divisional Scientific and Technical Merit Review System. The rationale for initiating a change in the DRR review system was based on the traditional but recently restated policy of the NIH that there should be a rational separation of scientific and technical merit review from program operations. Such a system has as its stated goals:

- increasing the mutuality of program knowledge and a sharing utilization of health scientist administrator personnel among the five DRR programs, and

- decreasing the subtle but inherent conflict of interest involved in having the four roles of program planning, program development, application review, and program evaluation under the direct leadership of an individual program director.

The major features of the newly implemented review system are as follows:

1. Overall responsibility for the initial, scientific, and technical merit review of research (resource) and training grant applications assigned to the DRR for initial review rests with the Deputy Director, DRR. The Deputy Director also has the responsibility for overseeing review functions of the National Advisory Research Resources Council (NARRC).

2. Health scientist administrators, who are not the directors of DRR programs, have been selected as executive secretaries of the DRR Initial Review Committees.

3. Executive secretaries have responsibilities relating to the review functions of the committees; Program Directors have responsibilities relating to the program advisory functions of the committees.

It is the intent of the Division to seek authority to establish a program advisory committee for the Biotechnology Resources Program. Although the Program has no review activities, the lack of an established program committee results in a serious deficiency of high quality advice for the Program staff.

Program staffing problems of a year ago have been significantly ameliorated by the selection of Dr. Suzanne Stimler as the Director of the Biotechnology Resources Program, Dr. Francis Kendrick as Director of the Biomedical Research Support Program, and Dr. Leo Whitehair as Director of the Primate Research Centers Section of the Animal Resources Program. Several additional health scientist administrators have been added to the various Program Branches.

The Deputy Director has served as the project officer on the contract with Bolt Beranek and Newman, Inc., of Boston. Bolt Beranek and Newman has the responsibility to coordinate the evaluation of the scientific mission of the Division. The contract was let on July 15, 1975, and is scheduled to

terminate on October 1, 1976. The initial efforts of the contractor dealt with the selection, following the concurrence of the Deputy Director, NIH, of a 15-member evaluation panel. The panelists are:

Dr. Irwin W. Sizer
Co-Chairperson
Massachusetts Institute of Technology

Dr. Linda S. Wilson
Co-Chairperson
Associate Vice Chancellor for Research
The Graduate College
University of Illinois

Dr. Carleton B. Chapman
President
The Commonwealth Fund

Dr. Clifton O. Dummett
Associate Dean for Extramural Affairs
School of Dentistry
University of Southern California

Dr. Marvin A. Jackson
Chairman
Department of Pathology
Howard University College of Medicine

Mr. Jonathan Leff
Director of Special Publications
Consumers' Union

Dr. Robert R. Marshak
Chairman
Department of Medicine
School of Veterinary Medicine
University of Pennsylvania

Dr. Bruce H. McCormick
Professor
Department of Information Engineering
University of Illinois at Chicago Circle

Dr. William D. McElroy
Chancellor
University of California at San Diego

Dr. Joseph L. Melnick
Chairman
Department of Virology and Epidemiology
Baylor College of Medicine

Dr. Frederick Mosteller
Chairman
Department of Statistics
Harvard University

Dr. Richard M. Restak
(M.D.-Private Practice in Neurology)

Dr. Henry W. Riecken
Professor
Department of Behavioral Medicine
University of Pennsylvania School of Medicine

Dr. Elizabeth S. Russell
Senior Staff Scientist
Jackson Laboratories

Dr. James B. Wyngaarden
Chairman
Department of Medicine
Duke University Medical Center

The first meeting of the Panel, held in October 1975, was devoted to present
tions by DRR staff concerning the Division's programs and organization. The
Director and Deputy Director of NIH also met with the panel and discussed th
purposes of the evaluation study. Several expert consultants for each of th
programs were selected to supplement the subsequent tasks of the panelists.

Primary and secondary data have been provided the panelists, which in additio
to the information they have obtained through a considerable number of
institutional visits and interviews with NIH officials, will form the basis
the panel's report.

We anticipate that the Mission Study Report will serve as a very useful
document for staff and Council dialogue in the development of a Five-Year Pl
for the Division.

DRR BRANCH REPORTS

Fiscal Year 1976 Annual Report
Animal Resources Program
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Branch (ARB) is to support resource projects that provide, or enable biomedical scientists to effectively use, animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The Branch objectives are accomplished through a Primate Research Centers Program a Laboratory Animal Sciences Program, and Research Contracts.

PRIMATE RESEARCH CENTERS PROGRAM

The seven Primate Research Centers were established with Federal funds in the early 1960's to provide unique research environments for the use of nonhuman primates in many important areas of biomedical research. The core operations of the Centers are funded by grants from the Animal Resources Branch. The Centers have continued to make many significant contributions in the forefront of biomedical primatology. During the past year, many important contributions were made in areas including reproductive biology, neural control of the cardiovascular system, lung diseases induced by environmental agents, infectious diseases, nutritional and metaboloic diseases, and behavioral sciences.

Core financial support provided for the Centers by this program has permitted the 132 core staff scientists to conduct biomedical research on a total of 98 grants and contracts with total funding of $5.214 million. In addition, the 253 collaborative and affiliated scientists from a number of universities utilized the facilities and other resources of the primate Research Centers to conduct investigative research on 120 grants and contracts with total funding of $7.092 million. The Centers also provided the research environment for 163 graduate students to pursue their thesis research. The program provided salary support for 164 doctoral level staff and technical and administrative personnel.

During the past year, problems associated with obtaining sufficient numbers of nonhuman primates for biomedical research use have remained at a critical stage. Therefore, domestic breeding of the various primate species most useful to the Centers' research program has continued to receive special emphasis. Approximately 1,100 infant primates and fetuses were produced by the Centers during the year, representing approximately 50 percent of their annual requirements. Small nuclear breeding colonies of approximately 24 less commonly used primate species were also maintained to assure their survival for future research purposes.

The missions of the seven Centers and selected examples of their research activities are as follows:

OREGON PRIMATE RESEARCH CENTER

The missions of this Center are in the areas of reproductive biology, and cardiovascular, metabolic and immune disease. An example of their research accomplishments is as follows:

Cholesterol Gallstones in Squirrel Monkeys:

Investigations have shown that squirrel monkeys (Saimiri sciureus) develop cholesterol gallstones when fed several different types of semipurified diets. Studies have been made to determine the factors that are associated with gallstone formation and of the mechanisms involved in their formation. Diets containing cholesterol and safflower oil (unsaturated fat) were found to consistently cause gallstone formation. Male castrates were noted to be particularly susceptible to gallstone formation, although no difference was detected in gallstone prevalence between normal, intact male and female animals. Studies also revealed that the highest rates of cholesterol absorption were consistently found in animals fed a combination of safflower oil and cholesterol.

DELTA PRIMATE RESEARCH CENTER

This Center's primary mission is in the area of infectious diseases research. An example of their accomplishments during the past year is as follows:

Filariae of Man in Primates:

Studies have been made to determine the relationship of certain types of filariae (nematode endoparasites) of several nonhuman primate species (chimpanzee, rhesus monkey, patas monkey) to several types of human filariae. Comparative morphological studies of these human and nonhuman primate endoparasites were made. The "perstans-like" filaria of the chimpanzee was shown to be virtually identical to Dipetalonema perstans (filaria) of man in the same geographical area (Cameroon, West Africa). The parasite in the chimpanzee offers an excellent model for the study of the behavior and other biological aspects of the human parasite. It also provides an opportunity to investigate the pathological changes which may be produced by the parasite in its definitive host. Other studies involved the successful experimental transfer of a human strain of Loa loa (threadlike filarial roundworm of West Africa) via infected vectors (Chrysops, a tropical tabanid fly) to produce patent infections in three species of monkeys. Work is now focused on the development and onset and course of patency, as well as the involvement of the spleen in suppression of peripheral microfilaremia.

YERKES PRIMATE RESEARCH CENTER

The major missions of the Yerkes Center are in the areas of neural and behavioral research, immunology, Great Ape reproductive physiology and the study of neoplastic diseases. The following is an example of these research activities:

Physiological Concomitants of Drug Abuse:

Investigations were focused on the diverse and varied effects which pharmacologic agents (drugs) can have on behavior of intact, conscious animals due to their actions on the central nervous system. This work demonstrates that several drugs (including d - amphetamine and chlorpromazine) can have marked effects on operant behavior in nonhuman primates (squirrel monkey and chimpanzee) when administered at doses comparable to those used in humans. The data indicated that the behavioral effect of the drugs was determined by the rate at which the behavior was ongoing prior to drug administration. The drugs, d - amphetamine and chlorpromazine increased the rate of behavior when it was low in rate prior to drug administration and decreased behavior rates that were high prior to drug administration. The effects of cocaine and morphine (alone or in combination with other drugs) were also studied in the squirrel monkey and chimpanzee. These drugs increased low rates and decreased high rates of behavior. Studies are in progress to determine the effects of cocaine on heart rate, mean systemic arterial blood pressure and body temperature.

WASHINGTON PRIMATE RESEARCH CENTER

The mission of this Center is neurophysiological research with particular relationship to control mechanisms of the cardiovascular system. In addition, the collaborative research program involves a large number of scientists of many biomedical research disciplines. An example of the research activities at this Center is as follows:

Central Nervous System and Endocrine Control of Temperature and Metabolism:

Studies were made to determine the response of chair-adapted male baboons to acute and sub-acute cold exposure. Measurements were made of various serum plasma and urinary hormone levels to assess the increase of thyroidal activity and activation of the hypothalamic-pituitary-thyroid axis by cold stress. Arterial blood pressure and heart rate (cardiovascular parameters) were also monitored during cold exposure and were noted to rise as core temperature fell. These latter findings suggested inhibition of the baroreceptor reflex due to the developing core hypothermia. In contrast to results found in other experimental animals (e.g., rat, goat), the nonhuman primate does not exhibit a prompt activation of the thyroid gland via hypothalamic

thyrotrophin-releasing-hormone (TRH) and pituitary thyrotrophin-secreting hormone (TSH). Rather, the first indication of hypothalamic stimulation of the pituitary-thyroid axis did not appear in the baboons until the third day of cold stress and moderate hypothermia.

WISCONSIN PRIMATE RESEARCH CENTER

The basic research missions of the Wisconsin Center are in the areas of primate behavior, reproduction, and neuroscience. An example of research activities at this Center is as follows:

Prenatal Androgens and the Development of Behavioral Sex Differences:

Studies were made with rhesus monkeys to assess the relative effectiveness of two different androgens (male sex hormones); namely, testosterone and dihydrotestosterone, on the development of behavioral sex differences. Since both hormones are active in the display of adult sexual behavior, efforts were made to determine whether dihydrotestosterone is active in the prenatal organization of sexually dimorphic behaviors. Twelve pseudohermaphrodites were studied. Some of these animals were produced by exposure prenatally to varied doses of testosterone propionate (TP) over different time periods, while other animals were exposed prenatally to varied doses and time treatments with dihydrotestosterone propionate (DHTP). The findings clearly indicate that prenatal treatment with DHTP is effective in altering morphological and behavioral traits toward the masculine form. However, external genitalia of the animals were not well masculinized. Another finding from this study is that the mother-peer rearing condition does allow early and full development of mounting behavior in both male rhesus and rhesus pseudohermaphrodites.

NEW ENGLAND PRIMATE RESEARCH CENTER

The major core program mission of this Center is in the areas of infectious diseases and primate pathology. In addition, a large number of collaborating scientists conduct a major portion of their research activities at the Center. An example of the research projects is as follows:

Effect of Herpesvirus saimiri in Human Cell Cultures:

Human cell cultures were successfully infected with Herpesvirus saimiri. The virus was found to multiply in these cell cultures but did not induce a complete cytolytic infection. The infectious virus was recovered up to 187 days after initial infection. Cell fusion techniques resulted in the recovery of infectious virus from the latently infected human cell cultures 347 days after initial infection. Therefore, it was fully demonstrated that this primate oncogenic virus was capable of infecting human cell cultures, first as a persistent infection and later as a latent infection.

CALIFORNIA PRIMATE RESEARCH CENTER

The mission of this Center is in the areas of environmental health sciences and infectious diseases. An example of their research activities is as follows:

Influence of Acid Aerosols on Production of Chronic Lung Disease:

Because of the prospects of greater use of sulfur-containing fossil fuels for energy needs in the future, comparative studies were made with three species (rhesus monkey, guinea pigs and rats) to assess the biological effects of sulfuric acid (H_2SO_4). The animals were continuously exposed to acid aerosols generated from vaporized sulfate (SO_3) entering a humidified airstream. Pathological studies on lung tissue from the animals following exposure revealed striking differences in species susceptibility to acid aerosol induced pulmonary damage. The respiratory tract of the rhesus monkey and rat were found to have a remarkable resistance to sulfuric acid induced morphological damage, in contrast to the extreme sensitivity of the respiratory airways of the guinea pig to acid aerosols.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants and contracts. Currently special program areas include support for animal colonies of unusual and special value for research; studies directed at finding animal models which are needed for research on human diseases; projects to assist institutions to comply with the legal and policy requirements for care of laboratory animals; laboratories for the diagnosis and control of disease of laboratory animals; research related to improving health care and determining environmental requirements of animals used in research; reference and information centers dealing with selected problems; and research training of specialists in the field of laboratory animal medicine. The Program awarded funds totaling $8.044 million in fiscal year 1976, which supported 73 discrete animal research and resources projects, 5 institutional fellowship programs, 4 individual fellowship awards, and 16 contracts.

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are (1) to define, characterize, and exploit the relevant biological attributes of selected animals which display potential for use in several areas of biomedical research; (2) to establish, improve, or expand special colonies of well characterized animals which are of proven value for specialized areas of biomedical research, but which are not generally available from other sources; and (3) to preserve unique and valuable stocks and strains of animals which may otherwise be lost due to particular circumstances.

Support for projects related to the establishment of special animal colonies and animal model development increased slightly from FY 1975 to $1,459,306, but the number of projects was decreased by 2 to a total of 19. During FY 1976, 13 of these resources provided support for 55 NIH funded research projects having a total funded value of $4,690,808. Support was provided to an additional 42 research projects which received funding from other sources in the amount of $1,115,901.

The majority of the currently active projects are related to vertebrate species such as rats, mice, guinea pigs, hamsters, dogs, cats, rabbits, nonhuman primates, armadillos, and amphibian species. However, interest in the development of models is not limited to vertebrates. For example, the research potential of several marine invertebrate species has led to support for their development as research resources. A contract is supporting the development of methods for rearing the sea hare in the laboratory. The sea hare is a marine mollusk with large neurons that is useful in neurophysiological research, but whose availability has been limited. During the last year, newly devised methods have been shown for the first time that production of these animals outside their native habitat is feasible.

The adoption of support by the categorical Institutes for resources that have been established provides continuing evidence that this program is fulfilling its intended purpose. For example, the NINDS recently assumed support of a cat breeding colony at the University of Alabama which had previously received program support as a laboratory animal resource. A high incidence of GM_1 gangliodosis was identified among the progeny of breeders in the colony. This disease was found to be identical to a progressive and fatal neurological disease of children (Derry's Disease) for which the provision of a suitable animal model proved to be an opportune development.

The exploration for new types of animal models has generally been directed towards those species or strains which show potential promise rather than toward generalized surveys of animal populations. However, the species represented in the variety of projects supported vividly illustrate that this effort has been extremely flexible and responsive to the need for animal models for biomedical research. Model exploration and development have continued to advance during the last year at the institutions where such efforts are being supported as the following examples indicate:

1. At the University of Alabama a diabetic mouse has been developed that has unique advantages over mice that have been previously used for studies of this disease. These mice breed well and have a life span comparable to normal mice. These attributes will facilitate the study of chronic disease effects. Continuing in the successful development of feline models for human neurological disorders, cats have been found with GM_2 gangliosidosis. Promising efforts are being made to breed cats with this disorder which appears to be identical to Tay-Sachs disease in humans. A basis has been established by the similarity between dwarfism in cattle and human mucopolysaccharidosis.

Tissue culture of biopsies from affected cattle is being used as a tool to determine the location of the metabolic defect that leads to the expression of this disease.

2. At Washington State University efforts are continuing to determine a dependable experimental method of eliciting seizures in dogs that have progressive canine epilepsy. Progress in determining that seizures may be related to defects in carbohydrate metabolism may provide valuable insight into the pathogenesis and control of this disorder. By backcrossing breeding techniques, efforts are being made to transfer the genetic characteristic in Persian cats that causes Chediak-Higashi syndrome to domestic shorthair cats. It appears likely that this effort will provide hardier and more prolific cats for the study of this disease. A disease with potential useful application as a human disease model was recently found in which the leukocytes of Irish Setters are deficient in their ability to destroy bacteria.

3. At Jackson Laboratory a number of new mutations have been found among the inbred strains of rabbits that are being developed and maintained there. These have included mutations for scolosis, histocompatibility loci, chondrodystrophy, lymphosarcoma, and hemolytic anemia.

4. Germfree derived Louvain and Lister strain rats at the Lobund Institute at Notre Dame University have been shown to have a high prevalance of immunocytomas and subsequently develop high levels of IgE immunoglobin. This characteristic could be useful in determining the role of IgE in allergic disorders. The most significant advances from this institution deal with the development of model systems for the study of neoplastic diseases. Heterogenic chimerism was recently accomplished by giving mouse bone marrow to germfree irradiated rats. This technique has potentially useful application in both research and cancer therapeutic methodology.

Improving the availability and increasing the body of knowledge concerning existing research animal models is a major area of interest in the program. The following examples illustrate accomplishments in this area during the past year:

1. At the University of Illinois a stock of complement (C-6) deficient rabbits obtained from NIH is continuing to be expanded. Selective breeding procedures are being focused on genes that play a significant role on in vivo cellular damage and wound healing.

2. New inbred strains of hamsters are being developed at MIT from 12 pairs of hamsters obtained from Syria in 1971. Since all hamsters currently being used in research have been derived from a single pair of animals imported years ago into the United States, this project promises to considerably expand the gene pool in hamsters used for research. Some of the evolving strains have reached the 10th

generation and characteristics of interest that have been observed include possible hereditary anomalies (opthalmic defects, deformities of the urogenital system, severe malocclusion), a dramatic coat coloring mutation, and differences from other hamsters in histocompatibility phenomena.

3. At the California Institute of Technology a longitudinal study of the sea urchin, Strongylocentrus purpulatus, in its natural marine habitat is being carried out to determine those factors that influence year round fertility in limited geographic areas. Practical application of the findings could favor laboratory breeding, promote a continuously available source of specimens, and lead to the development of appropriate conservation methods. The sea urchin has been shown to be an excellent model for the study of molecular events that occur during early embryonic development.

4. Amphibian resources at both the Louisiana State University and the University of Michigan are continuing to improve laboratory breeding techniques and produce animals that are free of the environmental variables and diseases that are common to wild caught animals. Michigan, which is the only place where leopard frogs have been successfully cultivated in the laboratory, produced 17,500 frogs during the report period and provided them to 287 investigators throughout the country.

5. Germfree resource laboratories located at both the University of Wisconsin and Louisiana State University have made significant progress in producing germfree dogs that can be used for breeding beyond one year of age. At the Louisiana resource, gnotobiotic rodents are playing essential roles in a number of NIH supported projects. These deal with the role of gastrointestinal flora in stress, the metabolic aspects of hemorrhage and endotoxin in irreversible shock, and the development of a vaccine for protection against Pseudomonas infection following severe burns.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Upgrading of existing animal facilities and development of new centralized animal resource programs has continued to be a major program area. Requests in this area usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program; however, they received increased emphasis beginning in FY 1972 when Congress appropriated an additional $1.5 million for this area. These funds were added to the regular budget to help research institutions achieve

compliance with the Animal Welfare Act of 1970 (P.L. 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued June 14, 1971) and the subsequent DHEW policy on "Animal Welfare" (issued May 14, 1973) also contributed to the overall response in this area. The following figures demonstrate progression of support:

	FY 71	FY 72	FY 73	FY 74	FY 75	FY 76*
No. of Projects	14	24	28	46	38	22
$ Awarded (in $1,000's)	673	2,169	2,318	3,217	2,582	1,285
Percentage of Budget	11%	35%	37%	55%	42%	24%

*estimate

The dramatic decrease in FY 1976 reflects the high turnover rate of projects in this area and the fact that relatively few new projects were approved during the current year. The number of new applications for developing institutional animal resource programs continued at approximately the same level as last year (FY 75 - 21, FY 76 - 18). Six of the 8 projects recommended for approval were funded. Over the past 5 years a total of 96 institutions have received improvement grants ($12.2 million). A substantial number of inquiries are still directed to this program area. Thus, it appears that the present level of activity will be maintained for at least the next several years.

DIAGNOSTIC LABORATORIES

The objectives of these laboratories are to provide for improved animal health programs through investigation of naturally occurring laboratory animal disease, to support indepth studies resulting in new information on disease processes and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources including tissues, slides, photographs, etc., for research and training in laboratory animal medicine and comparative pathology. There are 14 programs which are currently being supported ($1.440 million - 25% of LASP budget). A shortage of appropriately trained specialists (veterinary pathologists and microbiologists) has been a limiting factor, precluding any rapid establishment of new programs. However, one new laboratory was funded during FY 1975.

In addition to the service aspects of undergirding an institution's animal health program, the laboratories have been productive in terms of new information and techniques. Indepth studies of laboratory animal disease problems resulted in over 70 publications and presentations during the past year. The value of routine surveillance activities continues to be demonstrated. In particular, several laboratories have worked closely with commercial producers of laboratory animals. As a result of this activity, some producers are now, possibly for the first time, aware that they have serious disease problems. Because of the awareness of these problems, they are making preliminary plans to improve the disease status of their

research animals. One laboratory has been active in monitoring of a newly established rhesus monkey colony. A basic goal was to develop a colony free of Herpes B antibody by means of isolation and repeated serologic testing. This was considered desirable since the animals are used in long-term experiments involving manipulation around the head and mouth. The first documented case of systemic blastomycosis in a squirrel monkey was reported by another laboratory. The organism was tentatively identified as Blastomyces (Paracoccidiodes) brasiliensis, the etiologic agent of South American blastomycosis. The presence of organisms in the gastrointestinal tract suggests that a tissue phase could be excreted, posing a public health hazard. A naturally occurring cytauxzoonosis-like disease in cats was reported from another laboratory. This heretofore unreported disease of cats appeared to be relatively common in southwestern Missouri. It was characterized by fever, anorexia, anemia, icterus, dehydration and death. Previous reports of cytauxzoonosis have been associated with ruminants in South and East Africa where the vectors are ixodid ticks. Since cats for research purposes are often obtained from rural areas, the account of this disease should encourage others to look for naturally occurring cases in cats as well as in other animal species. Further field and laboratory studies are necessary to better define the clinical syndrome(s), to determine the vector, possible reservoir hosts, transmissibility among cats, and susceptibility of other species, including man and domestic livestock.

RESEARCH PROJECTS

The Program has provided support to a relatively small number of discrete research projects over the past several years. This may be summarized as follows:

	FY 72	FY 73	FY 74	FY 75	FY 76 (Est.)
Number of Projects	6	8	10	9	10
Awarded (in thousands)	449	593	591	490	462
Percentage of Total $	7%	10%	10%	8%	8%

Projects falling into this category generally have one of the following objectives: (1) to investigate the etiology, pathogenesis, and control of laboratory animal disease problems; and (2) to determine various environmental requirements of laboratory animals. For example, currently active projects include studies of transmissible atypical ileal hyperplasia in the hamster, definition of environmental conditions for laboratory animals, development of a vaccine to control feline viral rhinotracheitis, diagnosis and control of mammalian encephalitozoonosis, and application of mass air flow (MAF) for animal isolation and quarantine. Work on the latter project has demonstrated that MAF under prescribed conditions will significantly reduce airborne infection using polyoma virus as a marker organism. Results of controlled studies showed that MAF decreased the microbial aerosols generated during cage changing, even with vertical air

velocities as low as 15 feet/minute. In addition to vertical air velocity, the intra-cage distance influenced airborne polyoma virus infection. There was no significant difference in noise levels, weight gain per mouse, temperature, CO_2 and NH_3 concentration or number of technician hours between the mass air flow and control rooms. The cost of operating the motors and air conditioners in the MAF room was 17 times higher than in the control room. These results have been of practical importance already in the development of MAF animal facilities. Future efforts will examine the effect of less efficient filters and two air velocities (30 feet/minute for 3 hours during cage changing and 10 feet/minute the remaining time) to see if maintenance costs can be reduced.

RESEARCH CAREER DEVELOPMENT AWARDS

The Research Career Development Award (RCDA) program was initiated during the year. The RCDA provides salary support for individuals who have had at least three years postdoctoral experience and have demonstrated potential for development into creative independent investigators. A total of eight applications were considered during the year, of which five were recommended for approval by the initial review group. One award has been made to date. Others are pending; however, program relevance was marginal in the case of several of this first group of applications. The intent of this program is to increase the number of first rate investigators who have, as their career goal, research on laboratory animal resource problems.

REFERENCE CENTERS AND INFORMATION PROJECTS

The Program has continued to support several reference centers and information projects. Examples of these are:

1. A Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas. The Laboratory now has a working repository of over 60 virus reference reagents and reference antiserums. Ongoing activities of the project are designed to give information regarding the immune status of subhuman primates and the possible cause of outbreaks of overt diseases. Institutions throughout the country have taken advantage of this program. For example, during the past year, 46 laboratories submitted over 2,100 specimens for antibody surveys or virus isolation and identification.

2. The Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology (AFIP). The Registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds. Material has been made available to others and utilized for the preparation of exhibits, lantern and microscopic slide sets, and as the basis for a number of publications. A handbook entitled "Animal Models of Human Disease" has been

prepared for sale. Four fasciles covering 60 models plus an index have been published so far and a fifth is planned for 1976. An annual short course (3 days) in Comparative Pathology was offered for the third time in May 1976.

3. The Laboratory Primate Newsletter, which now has a mailing list of about 1,700 individuals and organizations. The Newsletter provide information on maintenance, breeding, and procurement of nonhuman primates for laboratory studies. It also serves as a general source of information through announcement of meetings, nomenclature changes, etc., and aids investigators by publishing requests for materials.

4. An Immunohematological Reference Center located at Michigan State University. This reference center was established to produce, standardize and unify the resources available that recognize red cell blood groups, histocompatibility antigens, and other immunogenetic markers in the dog. The canine erythrocyte blood group system has been operational for a number of years, and efforts during the past year focused on identification of new donor recipient pairs for production of additional established reagents and potentially new antisera that would expand the system. In the histocompatibility area efforts were directed towards production and characterization of a specific canine antilymphocyte sera and establishment of a battery of specific DL-A sera for typing prospective donor-recipient pairs for subsequent reagent production. It is envisioned that as subsequent proposals utilizing the center's resources are developed the activities can be largely supported on a fee for service basis.

MANPOWER DEVELOPMENT

Training in laboratory animal medicine is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

The Animal Resources Branch has supported research training programs in laboratory animal medicine since 1967. Six programs and approximately 16 trainees were supported during the current fiscal year. The programs are all located in medical research environments. Diagnostic laboratories are also supported in each of these locations, and the laboratory resources have provided major input to the training experience. In addition to the training grant mechanism, the Branch has supported research training through the award of individual postdoctoral fellowships (five currently active Fellows). In some cases, these individuals have enrolled in ARB training programs. Approximately half of the individuals seek more

specialized research training. These fellows have engaged in indepth studies in a discipline or specialty such as surgery, pathology, virology or physiology, through which they can contribute to research animal resources.

Currently available figures indicate that 122 trainees and fellows have completed training since the inception of training grants and fellowships in laboratory animal science and medicine. Forty (40) of these are employed by medical schools and 58 by other academic, research or governmental organizations. The majority (70) are functioning as directors or staff members of a vivarium; 43 are engaged in research or are obtaining additional training; and 9 are engaged in public health and other activities. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

Last summer the active training programs and diagnostic resources were encouraged to employ veterinary students during their summer break. Nine programs and approximately 22 students participated and the overall response was very encouraging. Critiques of the students involved and a description of their program were submitted to the Branch and in turn distributed to all the program directors. It is hoped that this work experience will result in greater knowledge and interest in the field of laboratory animal medicine by veterinary students. Development of a "pool" of such individuals for future postdoctoral training should result in long-term benefits to the field.

In the fall of 1974, a new National Research Service Award Program was announced. This program replaced all previous training authorities which terminated July 12, 1974, with the passage of the National Research Service (NRS) Awards Act (Public Law 93-348). As currently active training programs reach the end of their project period, they will have to compete under the provisions of the new authority. The main changes in the new authority are a requirement for recipients (institutional or individual fellows) of NRS Awards to engage in biomedical research or teaching for a period equal to their period of support and a limitation of 25% of the total award for other than trainee costs (institutional programs). Two active training programs were renewed under this new authority beginning July 1, 1975. Five institutional programs, including two currently supported training grants, are competing this year for possible funding beginning July 1, 1976.

RESEARCH CONTRACTS

The Animal Resources Branch has used the research contract mechanism as an adjunct to its resource grant programs to support specific essential services or to initiate activity in vital resource areas that have not responded or are not eligible to respond to the grant mechanism. Research contract funds for ARB in FY 1976 were about $1,900,000. Sixteen projects were supported. These contract projects are in the following areas:

PARTIAL SUPPORT FOR THE INSTITUTE OF LABORATORY ANIMAL RESOURCES

The Institute of Laboratory Animal Resources (ILAR) is a subsidiary of the National Academy of Sciences, established as a coordinating agency to disseminate information, survey existing and required animal resources, establish standards and promote education in the field of laboratory animal science. Since July 1953, ILAR has received financial support from NIH. These activities are a valuable adjunct to the Animal Resources Branch program. The ILAR meets ARB needs for writing standards and guidelines for animal facilities and care, furnishing information on sources and users of laboratory animals, and providing survey information on the status of animal resources. Special activities include an information service on the sources and availability of over 450 animal models and genetic stocks and a field survey on the abundance and distribution of primates of biomedical interest in selected areas in South America. A symposium on "The Future of Animals, Cells, Models, and Systems in Research, Development, Testing, and Education," was held. The symposium exposed the advantages and limitations of the research subjects and methods discussed. Another special activity funded this fiscal year and scheduled for September 1976, is a symposium on housing of laboratory animals. It is expected that this symposium will bring together the latest information on the design and construction of laboratory animal facilities.

AMERICAN ASSOCIATION FOR ACCREDITATION OF LABORATORY ANIMAL CARE (AAALAC)

The Animal Resources Branch is providing, through a small contract, partial support for site visits that are conducted as part of the AAALAC accreditation program. This effort is important to maintain quality in the accreditation program. NIH officially recognizes AAALAC accreditation as meeting the requirements of its policy on the care and treatment of laboratory animals.

LABORATORY ANIMAL NUTRITION

A contract has been awarded to Committee on Animal Nutrition of the National Academy of Sciences to prepare two publications dealing with the nutrient requirements of laboratory animals. One publication will be on common laboratory rodents and the other on laboratory primates. In addition to specifying the nutrient requirements for these species, the publications are to include data on diet preparation, stability, storage, recommended feeding practices, and formulations of nutritionally adequate standard reference diets.

MARICULTURE OF MARINE INVERTEBRATES

The Animal Resources Branch has awarded two complementary contracts for laboratory breeding and rearing of Aplysia and related species. These marine mollusks are used in a variety of biomedical studies and are becoming increasingly difficult to obtain from nature. Progress in establishing laboratory culture of these species is being made by the contractors, the University of Hawaii and Pacific Biomarine, Inc. A third contract has been awarded to Shelter Island Oyster Company of

Long Island, NY to develop laboratory culture of squid. This animal is valuable for neurophysiological studies. It is abundant in nature, but can only be obtained during the warm season and wild caught animals are extremely difficult to maintain in the laboratory. It is hoped that laboratory culture of squid will be a means to overcome these problems.

LABORATORY FOR EXPERIMENTAL MEDICINE AND SURGERY IN PRIMATES

This primate resource is operated by New York University. It provides resource services to about 30 NIH funded investigators in the New York metropolitan area. Partial support is provided to help maintain the quality of the resource program.

CARIBBEAN PRIMATE CENTER

This primate resource includes a basic primate colony on the Puerto Rican mainland and semi-free ranging primate colonies on islands off the coast of Puerto Rico. The Center is a valuable resource for research on social behavior and neurologic behavioral relationships and is becoming an important breeding center. The Bureau of Biologics, FDA, the National Institute of Neurological and Communicative Disorders and Stroke, and the Animal Resources Branch all have primate production projects at this Center.

PRIMATE SUPPLY

The Animal Resources Branch at the end of the fiscal year will have 6 contracts for domestic breeding of nonhuman primates. In addition there is one small contract with an investigator at the University of South Carolina to search for semi-free ranging breeding sites in Southeastern United States. These contracts are part of the effort to assure a supply of primates for essential biomedical activities in the face of drastically curtailed importation of wild caught animals. Three contractors (Charles River Breeding Laboratories, Hazelton Laboratories, and Litton Bionetics) are breeding rhesus monkeys. The goal of the three colonies together is to produce 1,900 animals annually. We hope to attain this goal in 2 or 3 years. These contractors currently have on hand 2,600 breeders or potential breeders. Six hundred animals were born in FY 1976. A fourth contract to breed rhesus and/or cynomolgus monkeys will be added late in the fiscal year. There are two contracts to breed squirrel monkeys which are just completing their first year. These contractors (University of Puerto Rico Caribbean Primate Center, Bowman Gray School of Medicine) are supposed to be producing 400 offspring annually in 4 years. They have obtained 390 breeders or potential breeders, and this past year 12 offspring were born.

ADMINISTRATION

A considerable amount of time was devoted to reorganization of grants management, review activities, and program relationships within the Division. Accompanying these changes, minor shifts were made within the Animal Resources Branch. The Director of the Primate Centers program (Dr. Goodwin) retired late in fiscal year 1975. A Health Scientist

Administrator from the Laboratory Animal Sciences program (Dr. Whitehair) was named Director of the Primate Centers program. Another Health Scientist Administrator (Dr. Johnsen) was employed to be Executive Secretary of both the Animal Resources Advisory Committee and the Primate Centers Advisory Committee.

Issues surrounding the care and treatment of laboratory animals continues to be a focus of administrative activity. For example, this year we responded to 104 letters from Members of Congress regarding the care and use of animals in research.

A meeting of all of the Directors of ARB supported Diagnostic Laboratories was held in April 1976. The meeting provided for a very useful exchange of views on how to monitor animal quality. There was also a discussion of special capabilities which some laboratories could share with others. There was strong support for the plans of one laboratory to serve as a rodent virus reference center for the other laboratories.

Table I - Primate Research Centers Program Applications - FY 1976

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	1	1,137,367	-	-	-	-
Renewal	3	5,769,652	3	5,801,662	3	5,485,906
Supplemental	-	-	-	-	-	-
Continuation	4	7,919,990	4	8,020,993	4	7,018,094
Totals	8	14,827,009	7	13,822,655	7	12,504,000

[1] Direct Costs Only
[2] Includes Indirect Costs

Table II - Laboratory Animal Sciences Program Applications - FY 1976

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	44	3,899,501	22	1,757,248	13	1,329,100
Renewal	11	945,821	6	458,088	7	879,456[3]
Supplemental	5	254,900	5	246,649	5	301,159
Continuation	48	2,938,516	48	2,249,351	48	3,006,709
Totals	108	8,038,738	81	4,711,336	73	5,516,424

[1] Direct Costs Only
[2] Includes Indirect Costs
[3] Includes 1 prior year approval at $181,958

Table III - Training Grant Applications in Laboratory Animal Medicine - FY 1976

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	5	333,597	5	273,000	2	107,000
Renewal	-	-	-	-	-	-
Supplemental	-	-	-	-	-	-
Continuation	3	239,539	3	207,676	3	170,000
Totals	8	573,136	8	480,676	5	277,000

[1] Direct Costs Only
[2] Includes Indirect Costs

Table IV - Fellowship Applications in Laboratory Animal Science - FY 1976

Type	Number Received	Number Approved	Number Funded	Amount Funded
New	11	5	2	30,000
Renewal	-	-	-	-
Supplemental	-	-	-	-
Continuation	2	2	2	27,000
Totals	13	7	4	57,000

Table V - Laboratory Animal Sciences Program Resource and Research Grants Project Distribution, FY 1976

Type	Number Received	Amount Requested[1/]	Number Approved	Amount Approved[1/]	Number Funded	Amount Funded[2/3/]
Special Colonies & Models	34	2,526,199	27	1,679,535	24	1,814,897
Basic Improvement	32	2,707,450	23	1,276,792	21	1,289,563
Diagnostic Labs	14	1,198,886	12	876,249	13	1,458,480
Reference & Info	6	432,996	6	408,980	5	515,933
Resource Research	21	1,058,316	12	431,464	10	437,551
Primate Resources	1	114,891	1	38,316	-	-
Totals	108	8,038,738	81	4,711,336	73	5,516,424

[1/] Direct Costs Only
[2/] Includes Indirect Costs
[3/] Includes Prior Year Approvals

Fiscal Year 1976 Annual Report
Biotechnology Resources Program
Division of Research Resources

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INTRODUCTION

The Biotechnology Research Program (BRP) interfaces the knowledge of the physical sciences, mathematics, and engineering to biology and medicine for the advancement of biomedical research. The Program's resources combine the use of sophisticated and expensive instruments and equipment, complex methodologies, and unique human expertise to aid in the solution of important biomedical problems.

The Program has an array of diverse resources, all designed to meet one or more specific technological needs of biomedical research scientists. Emphasis at present is placed on the use of digital computation, mass spectroscopy, nuclear magnetic resonance spectroscopy and electron microscopy in biomedical research. As new, advanced technological tools become pertinent to health research, the Program makes these tools available to the biomedical community. The trend is for the resources to be specialized to specific research needs rather than to have general biomedical research application.

The scope of the activities in each Biotechnology Resource include: (1) providing services in the Resource's technology to the biomedical research community; (2) engaging in collaborative research arrangements with appropriate biomedical scientists; (3) engaging in core research and development activities in the resource's technology designed to provide new technological opportunities or increase the usefulness of existing technology for biomedical research; and (4) providing training opportunities for the research community so they can better understand the technology and apply it more effectively to their own research problems. By incorporating all four of these activities within a resource, the staff of the resource can provide current and appropriate response to the needs of the biomedical researchers.

BASIC DATA ON THE PROGRAM

Types of Biotechnology Resources

The Program supported 51 resource grants, 3 resource-related research project grants and 5 contracts during FY 1976. The varied technologies the

Biotechnology Resources provide the biomedical community are classified as follows:

Type	Number	$ Awarded FY 1976
Computer Resources	17	6,226,302
Biomedical Engineering Resources	3	505,076
Resources and Resource Related Research Projects for Characterization of Biological Structure and Function		
Mass Spectrometry	11	1,423,012
Nuclear Magnetic Resonance	10	1,098,761
Electron Spin Resonance	1	325,714
Biomedical Kinetics	1	a
Electron Microscopy	7	872,325
Biomaterials Resources	4	150,212

(a received no FY 1976 funds.)

The aggregate annual level for the grant and contract activities is approximately $12 million. A listing of the BRP-sponsored grants is given in Table I. Brief descriptions of the capabilities and research emphasis or applications for each project are also given in Table I. Table II lists the contracts funded by the Program in FY 1976.

It is particularly interesting to view the Program in historical perspective. In 1967, for example, 61 resources were supported at a cost of about $12 million. These resources fell into the following categories:

48 computer resources
10 biological structure characterization resources
3 biomaterials resources.

Both the numbers and the substantive nature of the resources have changed considerably during the intervening years, especially in the computer resources category. Compared to the 28 batch-processing or off-line, general-purpose computer installations in 1967, the Program has only one resource of this type in 1976. The computer resources supported now are specialized rather than general purpose. They provide such capabilities as interactive computer graphics, on line real-time interactive use with remote access through computer networks and image processing and analysis.

Rapid and far-reaching change is not limited to the computer resource category. In 1967 only two types of biological structure characterization resources were supported. These were nuclear magnetic resonance and mass spectrometry. In addition to these two types the Program now supports an electron spin resonance resource, a resource for fast biomedical kinetics research and electron microscopy resources which include million-volt electron microscope resources, scanning transmission electron microscopes (STEM) resources for high resolution structure studies and an electron microprobe

TABLE I

BRP-Funded Grants During FY 1976
As of May 31, 1976

Number	Principal Investigator and Institution	Title	Capability	Research Emphasis or Applications	FY1976 $ Award	Cumulative $ Awards
			Computer Resources			
RR-3-15	Wilfrid J. Dixon, Ph.D. Univ. of Ca. Los Angeles	Health Sciences Computing Facility	Batch processing, time share, graphics	Biostatistical research, modeling, cell cycle dynamics	1,446,048	20,955,976
RR-7-13	Earl H. Wood, M.D. Mayo Foundation Rochester, Minn.	Computer Processing in Biomedical Systems	Image processing and analysis	Non-invasive monitoring of cardiac function via roentgen video densitrometry	410,784	5,064,520
RR-15-14	Martin Pring, Ph.D. Univ. of Pa. Philadelphia	Medical School Computer Facility	Time sharing and batch processing	Biomedical kinetics modeling	314,302	3,917,436
RR-249-11	William S. Rhode, Ph.D. Univ. of Wis. Madison	Support of Laboratory Computer Resources	Stand-alone mini-computers	On-line real-time control of neurophysiology experiments	264,459	2,513,066
RR-259-09S1	Allan H. Levy, M.D. Baylor College of Med. Houston, Tex.	Computational Research Center Program	Batch processing and teleprocessing	Patient record management	32,093	2,312,960
RR-267-10	Eugene Ackerman, Ph.D. Univ. of Minn. Minneapolis	Health Computer Resource	Batch processing and time-sharing	EKG analysis	*	2,801,234
RR-276-11	Ivan R. Neilsen, Ph.D. Loma Linda Univ, Loma Linda, Ca.	Scientific Computation Facility	Dedicated systems and time-sharing, on-line graphics	Computer assisted pulmonary function testing, EKG analysis, biomedical modeling	259,294	1,435,483 *

RR-326-09	Howard Moraff, Ph.D. Cornell Univ. Ithica, N.Y.	Cornell Veterinary Medical Computing Facility	On-line interactive laboratory computing	Acquisition and processing of neurophysiology data	a	632,025
RR-374-09	Theodore H. Kehl, Ph.D. Univ. of Wash. Seattle	Support for Physiology and Biophysics Computer	Experiments hard-wired to resource computers plus time-sharing	On-line control and analysis of physiology experiments	192,441	1,253,008
RR-396-09	Jermone R. Cox, Jr., Sc.D., Wash. Univ. St. Louis, Mo.	A Resource for Biomedical Computing	Dedicated computers and macromodule systems	Cardiac rhythm monitoring, biomolecular modeling	1,894,661	11,705,008
RR-442-07	Cyrus Levinthal, Ph.D. Columbia Univ. N.Y., N.Y.	Computer Resource for Image Processing and displays	Image processing and interactive graphics	Neuro-anatomical modeling, biomolecular modeling	238,539	1,517,112
RR-576-05	John Patterson, Ph.D. Pa. State Univ. Hershey, Pa.	Biomedical Computing Resource	Remote entry to institution computers, stand-alone mini-computers	On-line real-time control of biomolecular characterization devices	65,103	532,454
RR-578-05A1	Robert Langridge, Ph.D. Princeton Univ. Princeton, N. J.	Special Research Resource for Biomolecular Graphics	Stand-alone medium computer and graphics	Biomolecular modeling	a	1,009,678
RR-643-05	Saul Amarel, Sc.D. Rutgers Univ. New Brunswick, N.J.	Biotechnology Resource, Computers in Biomedicine	Access to time-sharing systems	Application of artificial intelligence to clinical decision making	407,260	1,393,201
RR-757-04	Joseph Kraut, Ph.D. Univ. of Ca. La Jolla	Resource for real-time Data Acquisition and Display	Computer-based automated laboratory systems	Biomolecular modeling, on-line acquisition of X-ray crystallography data	175,833	658,704
RR-785-03	Joshua Lederberg, Ph.D. Stanford Univ. Stanford, Ca.	Stanford Univ., Medical Experiment Computing Facility (SUMEX)	Remote access through computer networks	Applications of artificial intelligence in biology and and medicine	524,645	2,470,706
RR-898-02	Frederick Brooks University of N.C. Chapel Hill	Interactive Graphics for Molecular Studies	Interactive Computer Graphics	Biomolecular Modeling	a	191,930

Biomedical Engineering Resources

RR-12-14	Homer R. Warner, M.D. Univ. of Utah Salt Lake City	Biomedical Engineering Resource	Activities hardwired to resource computers	Patient monitoring, medical records management	171,214	2,822,280
RR-716-07, S1 and S2	Harold W. Shipton, C. Eng. Univ. of Iowa Iowa City	A Bioengineering Resource Facility	on-line real-time integration methods, on-line real-time display	Inter-facing laboratory instruments to computers, acquisition of electrophysiological data under computer control	76,443	324,374
RR-857-02	Wen H. Ko, Ph.D. Case Western Reserve Univ. Cleveland, Ohio	Biomedical Electronics Resource	Microelectronics fabrication, packaging and evaluation	Microelectronic devices for biological and clinical research	257,419	750,737

Resources for Characterization of Biological Structure and Function

Mass Spectrometry (MS)
Note: GC refers to Gas Chromatography

RR-273-11	Richard Abrams, Ph.D. Univ. of Pittsburgh Pittsburgh, Pa.	Mass Spectrometric Facility for Biomedical Studies	GC low resolution MS	Metabolic profiles	71,435	582,146
RR-317-09 and 09S1	Klaus Biemann, Ph.D. M.I.T., Cambridge, Mass.	Mass Spectrometry Facility for Biomedical Research	GC/high resolution MS	Drug identification, structure determination of unknown biomaterials	449,866	2,083,655
RR-330-09	David Rosenthal, Ph.D. Research Triangle Institute, Research Triangle Park, N.C.	Mass Spectrometry Center for Research Triangle Region	GC/high resolution MS	Structure determination of potential anti-tumor drugs	83,731	920,531
RR-355-08S1	Martin F. Semmelhack, Ph.D. Cornell Univ. Ithica, N.Y.	High Resolution Mass Spectrometer Facility	GC/Low and high resolution MS	Separation and detection of nucleosides	a	1,419,366
RR-356-08S1	Seymour R. Lipsky, M.D. Yale Univ. New Haven, Conn.	Physical Sciences Instrument Facility	Mass Spectrometry, NMR, High Performance chromatography	Separation and detection of nucleosides	a	1,419,366

RR-480-08	Charles C. Sweeley, Ph.D., Mich. State Univ., East Lansing	Michigan State Univ. Mass Spectrometer Facility	GC/low and high MS, field desorption MS	Structure determination of lipids, analysis of complex mixtures	128,541	764,067
RR-612-06	Carl Djerassi, Ph.D. Stanford Univ. Stanford, Ca.	Resource Related Research Computers and Chemistry	Computer software for interpretation of mass spectrometry data	Application of artificial intelligence to mass spectrometry	363,146	1,677,361
RR-665-03	Roger L. Foltz, Ph.D. Battelle Memorial Institute, Columbus, Ohio	Regional Medical Mass Spectrometry Resource	GC/low and high resolution MS, chemical ionization	Structure identification of natural products	61,326	216,810
RR-719-03	A.L. Burlingame, Ph.D. Univ. of Ca., Berkeley	Biomedical, Clinical Mass Spectrometry Resource	GC/low and high resolution MS	Vitamin Metabolism, pesticide identification	156,933	490,506
RR-862-03	Frank H. Field, Ph.D. Rockefeller Univ. N.Y., N.Y.	A Mass Spectrometric Biotechnology Resource	GC/low and high resolution MS, chemical ionization	Drug metabolism, drug assays, peptide sequencing	108,034	297,206
RR-954-01	William F. Holmes, Ph.D. Washington Univ. St. Louis, Mo.	A Resource for Biomedical Mass Spectrometry	GC/low resolution MS, chemical ionization	Drug and vitamin metabolism, inborn metabolic errors	a	320,374
Nuclear Magnetic Resonance (NMR)						
RR-292-11	Aksel A. Bothner-By, Ph.D., Mellon-Pittsburgh Carnegie Corp. Pittsburgh, Pa.	NMR Facility for Biomedical Studies	250 MHz NMR Spectrometer; ^{1}H, ^{2}H, ^{13}C, ^{19}F, ^{31}P, ^{11}B, ^{23}Na, ^{15}N, ^{33}S, ^{17}O ^{113}Cd, and others	Structure and function of hemoglobins, biological membranes, proteins	150,708	1,414,412
RR-542-06	George McDonald, Ph.D. Univ. of Pa. Philadelphia	Middle Atlantic Regional Spectrometer Facility	220 MHz, NMR Spectrometer; ^{1}H	Enzyme/substrate interaction mechanisms	72,143	704,007
RR-574-05	David M. Grant, Ph.D. Univ. of Utah Salt Lake City	Regional Research Facility in NMR	100 MHz NMR spectrometers; ^{1}H, ^{11}B, ^{13}C, ^{15}N, ^{19}F, ^{31}P	^{13}C labelled macromolecules	150,410	676,033

RR-636-03S1 and 04	Ephraim Friedman, M.D. Albert Einstein College of Medicine, Bronx, N.Y.	Biotechnology Resource for NMR Studies of Biomolecules	100 MHz NMR spectrometer; ^{1}H, ^{19}F, ^{13}C, ^{31}P, ^{23}Na	Structure and function of peptide hormones, drug-receptor interactions	66,241	396,342
RR-639-03	Jay A. Glasel, Ph.D. Univ. of Conn., Hartford	A New England Area NMR Research Resource	100 MHz NMR spectrometer; ^{1}H, ^{13}C, ^{2}H	Structure and function of peptides and hormones	55,347	293,458
RR-708-02	Nathan O. Kaplan, Ph.D. Univ. of Ca. La Jolla	Special Resources for NMR and Mass Spectrometry	220 MHz NMR spectrometer; ^{1}H, CFT-20 spectrometer-^{13}C, GC/low resolution MS	Metabolic studies, structure and function of biomolecules using stable isotopes	97,305	403,386
RR-711-03S1 and 04	Oleg Jardetzky, M.D. Stanford Univ. Stanford, Ca.	High Frequency NMR Biotechnology Resource	360 MHz NMR spectrometer; ^{1}H, ^{13}C	Structure and function of macromolecules	225,147	531,822
RR-798-02	Martin Saunders, Ph.D. Yale Univ. New Haven, Conn.	Southern New England High Field NMR Facility	270 MHz NMR spectrometer; ^{1}H, ^{2}H, ^{13}C	Structure of biological membranes, drug and hormones action	a	375,168
RR-892-01A1	Irwin D. Kuntz, Ph.D. Univ. of Ca. San Francisco	NMR Spectroscopy Resource	100 MHz NMR spectrometer;	Drug receptor interactions, lipid-protein interactions	a	222,468
RR-995-01	Leo J. Neuringer, Ph.D. M.I.T. Cambridge, Mass.	A National NMR Facility for Biomedical Research	270 MHz NMR spectrometer; ^{1}H, ^{13}C, ^{31}P	Structure and function of biomolecules	281,460	281,460
Electron Spin Resonance (ESR)						
RR-1008-01	Harold M. Swartz, M.D. Medical College of Wis. Milwaukee, Wis.	Biomedical ESR Spectroscopy Center	ENDOR, ELDOR Pulse ESR Spectrometers	Clinical applications of ESR, structure of free radicals in biological materials, enzyme kinetics	325,714	325,714
Biomedical Kinetics						
RR-886-01A1	Edward L. Powers, Ph.D. Univ. of Texas Austin, Texas	Center for Fast Kinetics Research	Pulsed 6MeV Van de Graff accelerator for radiolysis studies	Enzyme oxidase reactions, free radical processes in radiation biology	a	234,783

Electron Microscopy

RR-570-05S1 and 06	Hans Ris, Ph.D. Univ. of Wis. Madison	Electron Microscope Facility for Biomedical Research	1 MeV electron microscope	3-D structure of chromosomes, neuronal tissues, frozen tissues	110,644	1,122,888
RR-592-07	Keith R. Porter, Ph.D. Univ. of Colo. Boulder	High Voltage Electron Microscopsy logical Systems	I MeV electron microscope	3-D structure of whole-cultured cells, intracellular systems	194,663	1,499,600
RR-679-04	Claude P. Lechene, M.D. Harvard Medical School, Boston, Mass.	Biotechnology Resource in Electronprobe Microanalysis	CAMECA electron microprobe	Elemental composition of biological tissues	197,225	678,624
RR-715-04	Elliott N. Shaw, Ph.D. Assoc. Universities, Inc., Upton, N.Y.	Electron Microscope Facility	100 KV STEM	Under development	336,172	573,622
RR-754-01	Donald P. Parsons, Ph.D. Roswell Park Memorial Inst., Buffalo, N.Y.	Emulsions and Image Intensifier for HVEM	Image Processing	More sensitive systems for recording images in the I MeV Electron Microscope	a	128,153
RR-984-01S1	Albert V. Crewe, Ph.D. Univ. of Chicago Chicago, Ill.	Scanning Microscope Laboratory for General Faculty Use	40 KV STEM; Hitachi SEM, Coates-Welter SEM	Atomic resolution of single heavy atoms in biological materials	30,821	264,532
RR-1006-01	Thomas E. Hutchinson, Ph.D., Univ. of Minn. Minneapolis	Study of Frozen Hydrated Biological Materials	Transfer system and specimen stage for frozen specimens for the 1 MeV microscope	Frozen muscle, chromatin, and sperm	2,800	2,800

Biomaterials Resources

RR-657-01A1	Alfred P. Wolf, Ph.D. Assoc. Universities, Inc., Upton, N.Y.	A Program in Support of Nuclear Medicine	Production of radiochemicals with short-lived radionuclides	Nuclear Medicine	150,212	388,172
RR-759-02	Milton Helpern, M.D. New York Univ., N.Y., N.Y.	The Institute of Forensic Medicine as a Research Resource	Serology, toxicology, histology	Forensic pathology	a	120,270

RR-961-01	Donald A. Glaser, Ph.D. Univ. of Ca., Berkeley	Facility for Automated Experiments in Cell Biology	Large scale production of mutant cells	Mutants of microbial and animal cell cultures	a	1,326,000
RR-962-01	Nicholas A. Matwiyoff, Ph.D., Univ. of Ca., Los Alamos Sci. Lab., Los Alamos, N. Mex.	A National Stable Isotope Resource at Los Alamos	Provision of labelled compounds with stable isotopes of C, O, and N for biological research	Syntheses of labelled compounds with stable isotopes	a	216,840

Table II
BRP-Funded Contracts During FY 1976
As of May 31, 1976

Number	Project Director and Institution	Title	FY 1976 $ Award	Comulative $ Awards
NIH-70-4136	Robert M. Fisher, Ph.D. U.S. Steel Corp. Pittsburgh, Pa.	Supplying Services to Biomedical Scientists in the use of 1 MeV electron microscope	a	215,000
NO1-RR-5-2119	Arthur W. Nunnery, M.D. Univ. of Okla. Oklahoma City	Development of a Clinical Research Data Management and Analysis Role for Computers	34,373	117,998
NO1-RR-5-2117	T. G. Cristopher, M.D. Univ. of Wash. Seattle	Development of a Clinical Research Data Management and Analysis Role for Computers	a	114,176
NO1-RR-5-2118	H. K. Thompson, Jr., M.D. Baylor College of Medicine Houston, Texas	Development of a Clinical Research Data Management and Analysis Role for Computers	27,400	206,198
NO1-RR-5-2111	Gabriel F. Groner, Ph.D. The RAND Corp. Santa, Monica, Ca.	Development of a Clinical Research Data Management and Analysis Role for Computers	120,000	1,104,710
SB 3208(a)-75-C-590	Lucius Henderson Verve Research Corp. Bethesda, Md.	Provide Support Services for the Management of a Series of Workshops	a	349,800

resource for studies of the elemental composition of biological tissues at the cellular and sub-cellular level.

In 1967 the biomaterial resources provided substances such as enzymes, nucleic acids and various cellular and subcellular constituents to biomedical scientists. As these materials became available in the commercial market at reasonable prices, the resources were phased out. Today the biomaterial resources are directed toward serving the specialized needs of scientists. They provide materials that are not available from commercial sources, or if available, the cost of them is prohibitive to the scientists.

Currently the Program supports one resource that produces and provides to the research scientists large quantities of mutants of microbial and animal cell cultures for studies in a wide range of scientific fields. Another resource syntheses and provides to the research community labelled chemical compounds with stable isotopes of carbon, oxygen, and nitrogen for use in a variety of biomedical studies.

Biotechnology Resource Sharing

In 1967 the Biotechnology Resources were largely institutional in scope, with most resources serving only scientists residing within the host institution and some resources serving a limited region near the resource. Since that time, however, the requirements of the biomedical research scientists have increasingly been for more complex technology. This need coupled with the relative scarcity of talent to adequately exploit these technologies for biomedical research applications and the high cost of these technologies, led the Program to initiate and promote the establishment of resources that serve scientists on a national or on a broad regional level. The effort in resource sharing on this basis was started in FY 1974 and will continue for the foreseeable future. The objective of resource sharing is to effect a more nearly equitable distribution of highly specialized research support capabilities in the Nation and to provide access to these capabilities for researchers from institutions having limited biotechnology capabilities but strong biomedical research programs and compelling biotechnology needs.

The benefits of shared biotechnology resources are numerous. Some of these include: (1) the support of a larger and more varied body of investigators and problems, (2) fuller utilization of expensive instrumentation, (3) increased collaboration between investigators in different institutions who have research interests in common, and (4) the increase in numbers and quality of researchers and institutions able to benefit from sophisticated biotechnology approaches to their biomedical activities.

There are seven Biotechnology Resources that are national in scope. These resources have formalized mechanisms to deal with investigators residing outside the resource's host institution who wish to use the resource's technology and a method to solicite proposals from scientists who might use the resource's technologies.

Table III lists the national resources, their capabilities, and arrangements made for scientists to gain access to the resource. Because of the varied natures of sharable resources, specific appropriate administrative

arrangements are needed. Some of the computer biotechnology resources can be linked by telecommunication networks and are fairly readily adapted to the shared mode. Others such as the million volt electron microscope resources require the investigator and the problem be brought to the resource facility. In some cases the mail may be suitable as the provision of chemical compounds with labelled stable isotopes to scientists throughout the country.

Although shared biotechnology resource programs are still in comparative infancy, the potential for expansion is impressive. The experience gained in developing and managing these resources may well establish patterns of wide applicability in biomedical research.

TABLE III

National Biotechnology Resources

Principal Investigator and Institution	Resource Capability	Formal Sharing Mechanism
Hans Ris, Ph.D. Univ. of Wis. Madison	1 MeV Electron Microscope	Visiting scientists
Keith R. Porter, Ph.D. Univ. of Colo. Boulder	1 MeV Electron Microscope	Visiting scientists
Oleg Jardetzky, M. D. Stanford Univ. Stanford, Ca.	360 MHz NMR Spectrometer	Visiting scientists
Joshua Lederberg, Ph.D. Stanford Univ. Stanford, Ca.	Computer, PDP-10, tuned to needs of Artificial Intelligence research & communication tools	Computer networks
Wen H. Ko Case Western Reserve Univ. Cleveland, O.	Biomedical Engineering Resource in Microelectronics	Visiting scientists
Donald A. Glaser, Ph.D. Univ. of Ca. Berkeley	Large-scale production of mutants from microbial and animal cell cultures	Visiting scientists, mail
Nicholas A. Matwiyoff, Ph.D. Univ. of Ca. Los Alamos Scientific Lab. Los Alamos, N. M.	Labelled compounds with stable isotopes of C, O, N	Visiting scientists, mail

Support of Categorical Programs

One of the primary measures of accomplishment that can be applied to the Biotechnology Resources Program is the extent to which its sponsored activities markedly assist the various NIH categorical programs. With their cadres of highly skilled staff scientists and their specialized and often unique facilities, Biotechnology Resources are frequently the scene of productive encounters between experts in a given technology and experts in a given medical discipline. Table IV gives additional insight into the breadth and depth of this program on the health research supported by the DHEW.

Table IV lists the number of projects that made use of the Biotechnology Resources and the value of these projects in thousands of dollars of grant support for these projects. The data is presented for the NIH institutes and some of the Public Health Service Administrations. The distribution of research assisted by the Biotechnology Program reflects in part, how apportionment of research funds to the NIH institutes and other agencies brings research talent to a given area and how the staff of the Biotechnology Resources respond in meeting these demands.

TABLE IV

Number and Dollar Amount by NIH Institute and PHS Administrations of Projects Receiving Biotechnology Resource Support from 38 out of 45 Resources

Active During FY 1975

NIH Institute	Number of Projects	Dollar Value of Projects in $1,000
Allergy and Infectious Diseases	19	762
Arthritis, Metabolism and Digestive Diseases	47	3,752
Cancer	81	12,665
Child Health and Human Development	34	4,546
Dental Research	3	58
Environmental Health Services	1	135
Eye	4	535
General Medical Sciences	72	5,800
Heart and Lung	70	9,399
Neurological and Communicative Disorders and Stroke	48	5,159
National Library of Medicine	3	110
Total	382	42,921

TABLE IV (continued)

NIH Institute	Number of Projects	Dollar Value of Projects in $1,000
Other PHS Administration Components		
Alcohol, Drug Abuse and Mental Health Administration	59	10,615
Food and Drug Administration	3	217
Health Resources Administration	23	2,842
Grand total	529	56,595

NEW BIOTECHNOLOGY RESOURCES

(FY 1975 and FY 1976)

Biomaterials Resources

A unique biotechnology resource was funded at the University of California, Berkeley, in FY 1975 which has an automated system for producing, identifying, and isolating mutants of microbial and animal cell cultures on a large scale under varying controlled environmental conditions; primarily temperature, gaseous atmosphere, ionizing radiation and exposure to various chemicals. Up to 100 million cultures can be produced, processed and screened for mutants. The system which is computer-controlled is programmed to find and count all colonies, to measure their diameters and to characterize their visual appearance. It selects potential mutants and computer-directed manipulative tools transfer the selected colonies for further automatic testing.

The system at Berkeley will greatly facilitate the screening and search for hazardous substances in the fields of cancer, drugs, poisons, air pollution, and developmental defects. The resource provides service to the research community by filling requests for mutants and also participates in collaborative research projects with scientists throughout the country.

A biotechnology resource for stable isotope applications in biomedical science was established in FY 1975 at Los Alamos, New Mexico. The resource, which is the only one of its kind in the Program, makes use of the large amounts of stable isotopes of carbon, nitrogen, and oxygen produced as a by-product of the research program of the Energy Research and Development Administration at Los Alamos. The resource incorporates the isotopes by chemical and bio-synthetic methods into compounds needed for biomedical research and provides those labelled compounds to scientists on request. It also develops new synthetic methods for compounds not now available and collaborates with scientists who utilize compounds with stable isotopes in their research.

The resource will promote the use of stable isotopes for clinical applications such as tracer studies in metabolic disease and potential use in clinical diagnosis.

Resources for Characterization of Biological Structure and Function

Mass Spectrometry

A mass spectroscopy biotechnology resource was established at Washington University, St. Louis, in FY 1975. The resource will concentrate on applications of mass spectrometry in basic and clinical biochemistry. Examples of research that will make use of this technology include measurement of plasma levels of anti-depressant drugs in hospitalized patients with correlation of clinical effectiveness, measurement of platicizers found in post mortem heart tissue of neonotes that had been supported by intraveneous feeding using a plastic catheter and study of placental drug transfer of local anesthetics during childbirth.

Nuclear Magnetic Resonance

Two nuclear magnetic resonance resources were established; one at the University of California, San Francisco, in FY 75 and another at Massachusetts Institute of Technology in FY 1976. Both resources will use the technology to study the structure and the structure-function relationships of a broad class of biological materials.

The NMR resource at M. I. T. has three high resolution NMR spectrometers: (1) a 270 MHz NMR spectrometer with ^{1}H, ^{13}C and ^{31}P capabilities which is the main service spectrometer, (2) a 360 MHz spectrometer with versatile pulsed programming capability for use in study of liquids, membranes, and solids, and (3) a high frequency spectrometer to be constructed by the laboratory to operate at 532 MHz. The resource also receives funds from NSF for the construction and the purchase of these spectrometers. These spectrometers are available to scientists in the immediate Boston New England area and to other qualified scientists throughout the country.

The resource at the University of California, San Francisco Medical Center operates a 100 MHz spectrometer for the scientists in the Medical Center and in the San Francisco Bay area which have a need for this technology.

Electron Spin Resonance

An electron spin resonance resource was established at the Medical College of Wisconsin in FY 1976. This is the first ESR resource supported by the Program. The resource has the following major instruments available to scientists: Electron-nuclear double resonance (ENDOR), electron-electron double resonance (ELDOR), pulsed ESR and conventional ESR spectrometers with capacities to operate at three microwave frequencies (S-band, X-band, and Q-band) over a broad range of temperatures. A central trust of the resource will be the development of time-domain ESR technology for the purpose of studying important biological motions in the range of 10^{-3} to 10^{-6} sec, a time frame not readily accessible by other physicochemical methods. ESR will be used for studies of cellular functions and for methods for diagnosis of diseases. The resource is available to scientists in the surrounding region and throughout the country.

Biomedical Kinetics

A resource for fast kinetics research was established at the University of Texas, Austin, in FY 1975. This resource, which is the only one of its kind in the Program, has as its central equipment a pulsed electron source developed from a 6 MeV Van de Graff accelerator. Rapid reactions occurring after the disposition of the electrons in the biological systems studied are monitored by various fast detection techniques, and the data are analyzed by an on-line computer. The resource is available to scientists in the surrounding region and throughout the country.

Electron Microscopy

An electron microscopy resource was established at the University of Chicago in FY 1975. The resource has the following electron microscopes: (1) a 40 KeV scanning transmission electron microscope (STEM), developed in the principal investigator's laboratory, for high resolution work and for viewing single heavy atoms or small clumps of atoms in biological materials, (2) a Hitachi HSF-2 field emission scanning electron microscope capable of 30A resolution, and (3) Coates and Welter scanning electron microscope capable of 60A resolution. The resource is available to investigators in the Chicago area and elsewhere in the country.

Workshops Sponsored by the Biotechnology Resources Program

The BRP staff in seeking strength through the planning and promotion of sharing of highly specialized biotechnology research resources is undertaking a series of workshops to enrich this action. These workshops and related activities represent a potentially indispensable mechanism to facilitate the planning and communication associated with resource sharing. By assembling scientists in groups of various sizes, the BRP can simultaneously encourage interchange of ideas and draw upon expert technical advice. A continuing workshop series could be the principal forum through which BRP staff and the biomedical research community jointly bring about successful sharing of highly specialized research resources.

Workshops Conducted, Planned, or under Consideration By Biotechnology Resources Program

1. 1st Artificial Intelligence in Medicine, June 1975,
2. Indwelling Pressure Transducers, December 1975,
3. Biomedical Modeling - Biomedical Engineering, February 1976,
4. Nuclear Magnetic Resonance, March 1976,
5. Electron Microscopy at Atomic Resolution, March 1976,
6. Special Computer Hardware Development,
7. 2nd Artificial Intelligence in Medicine, June 1976,
8. Molecular Graphics, June 1976

The following discussion briefly describes each workshop that has been conducted and gives some insight of the predicted outcome of those conducted. Next year's annual report will provide an assessment of the impact of each workshop on its community.

Artificial Intelligence in Medicine (AIM) Workshop

The first of series of AIM workshops was held in 1975 and was designed to provide greater insight into existing and potential systems that apply methods of artificial intelligence (AI) to problems of a biomedical research and health care. This was the first occasion workers in this area of AI had met together. The dominant reaction of the participants was that discussion and communication between different groups were fruitful in lowering inter-disciplinary barriers and in disseminating the results of AIM research.

The theme of this workshop was "Knowledge-Based Systems in Biomedicine" and centered around discussions, demonstrations, and hand-on system experiences with existing systems for

- Medical knowledge modeling and decision-making with specific applications in glaucoma, infectious disease and internal medicine,
- Psychiatric simulation, psychological modeling, language analysis and common sense reasoning,
- Biomolecular characterization of organic molecules on the basis of chemical analysis, protein structure determination and chemical synthesis planning.

Plans for the second workshop in this series call for expansion with focus on active participation by those outside the present AIM community. The second AIM workshop was held in June 1976.

Workshop on Indwelling Pressure Transducers

This workshop was conducted in December 1975 to determine the availability and characteristics of pressure transducers with potential for application in health research. The state-of-the-art of solid state pressure sensors was described by presenters ranging from academic to commercial backgrounds. Health research needs that could be satisfied now and in the future were developed by selected leaders in health research. Two important observations were developed from this workshop.

- Sold state pressure transducers developed by academic microelectronics activities are clearly more advanced for health research application than those available from commercial sources. The distinguishing feature is that the range of pressure sensed by the academically developed devices are tailored to the pressures found in the physiologic systems.
- A critical attribute to long-term or chronic studies of physiological pressure variations is the stability of the zero pressure indication whose drift has long been

an impediment to utilization of feedback systems involving pressures as either the controlled or controlling variables in assisting or rehabilitating homeostasis.

The projections developed by the participants of this workshop indicate that pressure transducers suitable in all respects for long-term implant will be available on experimental basis late in 1976. Also, there is a clear expectation that these microelectronics activities will manage to reach this same level of technical maturity in implantable pCO_2, PO_2, PH_2, PO_2, force, and perhaps gas chromotography sensors within a few years. It is unlikely the present microelectronics resources will be able to satisfy the needs of the investigative community as these advances mature and medical requirements are translated into engineering performance specifications.

Biomedical Modeling - Biomedical Engineering Workshop

Biomedical modeling is a process that effectively arranges knowledge. It leads to a strong sense of recognition of obscure relationships that are important in understanding pathosphysiological operation of human systems. A model can represent a tool for knowledge-development and has the potential for formally organizing knowledge for more effective application and dissemination. This workshop, conducted in February 1976, was an attempt to characterize the modeling discipline, to assess the maturity of their products and to assess the sharing and shareability of this knowledge base.

From this workshop it is quite clear that mathematical or systems analysis is a relatively private act and that sharing is generally limited to exchange of ideas through publication. It is also clear that models developed could be seen as belonging to a community of scientists to help researchers organize and advance their knowledge of disease and help clinicians apply that knowledge to the service of medicine.

To accomplish these aims, a national resource would be required to plan and to implement:

- General modeling tools
- Assessment of models by peer review and plan clinical validation
- Documentation of models and education of their users
- Promotion of collaborative activities between systems analysts and clinical investigators
- Methods for implementing hierarchial model structures and exploration of the implications of such structures.

It was also quite clear that such a research resource would of necessity be distributed both across the country and across institutions. The present models at several hierarchial levels (biomolecular dynamics, pathophysiological, causal and associative states of disease, and signs and symptoms) are largely built and studied in isolation within the community. Thus, a resource at a

single institution or single region is neither practical or acceptable to this community. The participants described a resource comprised of three different levels and kinds of elements: (1) Core facilities in multiple institutions, (2) various affiliated resources with unique capabilities linked to the core activity via a computer network, (3) a collaborating community which would provide the expertise in knowledge utilization and knowledge interpretation for the clinician, and (4) a management element charged with exercising the unused potential for modeling in understanding of disease processes and the causal relationships to be discovered between disease states and underlying pathophysiology.

Immediate plans call for review of report of this workshop, to more clearly define the resource's functions and organizations, and a possible characterization for establishment of such a resource.

Nuclear Magnetic Resonance Workshop

This workshop was held in March 1976. Its objectives were to: (1) assess future need for high frequency NMR resources, (2) address the specific problems and issues confronting NMR resources, (3) build and/or expand communication within the NMR user community, (4) develop a management plan for current and future NMR resources, and (5) develop a 5-year plan for maintenance and development of NMR resources.

The some fifty participants in the workshop made a series of recommendations on these issues. They felt there should be a limited orderly expansion based on scientific need in numbers of instruments of the 360 MHz class. They recommended that one or two instruments of the 500-600 MHz frequency be funded over the next 5-year period, assuming the current development activities in this area will lead to a commercial instrument in this frequency range. The participants felt a list should be published that gives information on the existing NMR facilities in the country in high field and medium field range. This list should be updated once a year and should contain information on the availability of the spectrometer to outside investigators. They also recommended that travel money be made available to investigators on a one-time basis to conduct feasibility studies on a particular NMR instrument.

This workshop was held jointly with the National Science Foundation and some of the recommendations were directed to this agency. A complete report of the workshop will be available next fiscal year.

Workshop on Electron Microscopy of Biological Materials at Atomic Resolution

This workshop was held in March 1976. Its objectives were to: (1) review current progress in specimen preparation and the techniques of microscopy that are necessary in order to obtain atomic resolution, (2) discuss future directions in electron optical methods which show the greatest promise for attaining instrumental resolution at the required level, (3) discuss what types of resources for high resolution electron microscopy are needed by the scientific community.

The workshop participants identified a number of biological structural problems and then identified techniques that need to be developed or applied to solve these problems. Preparative techniques, image analyses and reconstruction techniques are some of the areas that need further development. A complete report of the workshop will be available next fiscal year.

Workshop on Special Computer Hardware Development for the Biomedical Research Community

Latest developments in computer hardware advances indicate that processing units with unique capabilities (floating point processors, file management processors, etc.) are capable of competing with the supercomputers of yesterday at ever-reducing costs. The falling costs of hardware reduces the pressure to use every piece of circuitry with maximum efficiency. Consequently, it is becoming more and more feasible for hardware to remain idle a major portion of time. The greatest problem arises when such distributed systems will be realized under a central control. The software requirements for dynamic allocation of such a distributed ensemble of unique processors performing dedicated tasks is not now well understood. Thus, it is more likely that data and flow control will be managed by the cross point switching approach. Compilers and applications programs will move from software to dedicated hardware systems.

The participants of this workshop, which was held in May 1976, elected to carry this communication to their biomedical computer colleagues and to produce a substantial publication outlining the continuing advances, opportunities and resources available to the community.

The CLINFO Project

CLINFO (Clinical Information) is a project designed to characterize the processes of clinical investigation and to facilitate such investigation where possible with computer technology. The project is being effected by a consortium of four contractors. This project was initiated in FY 1972.

One of the contractors (The RAND Corporation) is responsible for the information science and computer technology components of the work. The other three contractors (Baylor College of Medicine, The University of Washington, and the University of Oklahoma) provide knowledge of clinical investigation in general and the milieu of General Clinical Research Centers in particular. DRR staff, drawn from both the General Clinical Research Centers Program and the Biotechnology Resources Program, provide continuing direction for the project.

In the first phase of the project the Consortium of contractors demonstrated that clinical investigators, the major users of General Clinical Research Centers, have difficulty in organizing, storing, retrieving and analyzing their research data. While many of these investigators have access to computing facilities which theoretically might alleviate their problems, they generally do not understand how to use these facilities, do not have support personnel who would help them use the facilities, and otherwise have difficulty in using these facilities because of technical and fiscal instabilities

which are not under their control. Although there is a great deal of commonality among the investigators and among the General Clinical Research Centers, and there are a number of computer systems which deal with some aspects of the management and analysis of the data, there is no computer system available which can be used to effectively deal with the clinical investigator's problems in his environment. Furthermore, many investigators indicate that if they had a suitable data management and analysis computer system available to them, it could benefit them by reducing the duration of their studies and increasing the number of their publishable results.

In December 1975 the DRR initiated the second phase of the CLINFO project which deals with (a) implementing a multi-user, minicomputer-based system to help clinical investigators collect, organize, store, retrieve and analyze their research data (the CLINFO Tool) and (b) deploying this Tool at up to three selected General Research Clinical Centers.

The Clinical Centers selected for the first two CLINFO Tools are at two of the clinical investigator contractors who participated in the Inquiry Phase of CLINFO; namely Baylor College of Medicine and The University of Washington. Each of the sites has a senior clinician serving as Project Director and a systems manager trained by the RAND Corporation to handle the operational aspects of the Tool. In 1976, a third site for a CLINFO Tool will be selected in a nationally competitive basis if the first two installations are judged successful.

The second phase of the project will be funded over a three-year period. At the end of the second phase, this project should have produced the following:

- a tested and practical system which can continue to function at the sites;
- a knowledge of the benefits of the system and the continuing needs of clinical research not satisfied by the system;
- information about requirements for on-site personnel and continuing centralized function;
- knowledge of the changes produced by this system and a prediction of the future needs for computer facilitation of clinical investigation; and
- tested system capabilities and specifications for CLINFO systems which can be diffused commercially with greatly reduced costs for either a single user system or multi-user systems.

Fiscal Year 1976 Annual Report
Chemical/Biological Information-Handling Program
Division of Research Resources

INTRODUCTION

During Fiscal Year 1976, the Chemical/Biological Information-Handling (CBIH) Program continued to place its emphasis on the operation and further development of the PROPHET System - a unique national computer resource for the study of drug action mechanisms and other chemical/biological interrelationships. The PROPHET user community was expanded to include over 100 individual scientists at 12 sites throughout the nation and new information-handling capabilities were introduced into the System. In a wide variety of ways, the availability of PROPHET once again enabled users to explore hypotheses that they would find impractical, if not impossible, to consider in the absence of such a highly specialized and powerful research tool. This report summarizes the status of this novel multi-institutional cooperative endeavor as of June 1976.

THE CBIH PROGRAM

The goal of the CBIH Program is simply stated:

> assist the biomedical research community to employ modern computer-based information-handling concepts and methods in its efforts to place knowledge about chemical/biological interactions on an improved theoretical base.

Since drug actions and related phenomena manifest themselves at essentially every level of physiological organization from the single enzyme to the total organism, this goal is relevant across the spectrum from molecular biology to patient care. Since studies of drug effects and analogous processes occur in essentially every categorical disease area, this goal is important for every major component of the National Institutes of Health (NIH) and the Alcoholism, Drug Abuse, and Mental Health Administration (ADAMHA).

There also are important near term benefits from pursuit of this goal. By furnishing individual laboratory and clinical investigators with powerful computer tools which they can shape for their research, the Program helps them to enhance the utility of their own data and other information--often in dramatic ways. By concentrating on types of tools that are not generally available via traditional research facilities (such as computer centers, medical libraries, desk top calculators, and real time mini-computers), the Program fills an important and otherwise unoccupied portion of the spectrum of biomedical research services. And by focusing interest on computer-oriented methods for organizing, representing, and communicating biomedical information, the Program encourages research by those who wish to advance our predictive capabilities and to lay the scientific and technological groundwork for future information systems.

In pursuing its goal, the CBIH Program is guided by a three-task strategy:

1. develop standardized yet flexible computer-based tools with which

laboratory and clinical investigators can represent, organize, manipulate, and communicate their research data and other information in the most scientifically meaningful ways:

2. make these tools available to qualified members of the national community of scientists who are studying the mechanisms of drug action and analogous phenomena; and

3. collaborate with the users of these tools to refine existing methodologies and identify needs for new ones.

For task 1 these tools must be sufficiently easy-to-use so that the need for a technical intermediary between scientist and computer is the exception rather than the rule. For task 2 these tools must be made available to as large a user community as fiscal and manpower resources allow. For task 3 the collaborations must be in-depth and of long duration. Undertaking these three tasks in this manner seems to be the most fruitful way to establish the nexus between biomedicine and computer science that achievement of the Program's goal demands.

THE PROPHET SYSTEM

The heart of the above three-task strategy is a unique research resource called the PROPHET System. It consists of a highly skilled staff; a remotely accessible, time-shared computer facility; and a multifaceted, ever-evolving computer program specifically oriented toward the information-handling problems of those who study chemical/biological interrelationships. Driven by the stated and perceived needs of biomedical scientists and drawing upon the rapidly advancing state-of-the-art of computer science and technology, the resource staff carries out the continuing design and development of PROPHET's hardware/software complex. Furthermore, the resource staff employs the dedicated computer facility as a medium for making the PROPHET hardware and software available as a research service to a constantly growing user community distributed throughout the nation. This arrangement tends to insure that users' needs and experiences are the principal stimuli determining how PROPHET grows and changes; this arrangement also encourages the staff to integrate new and improved information-handling techniques into the PROPHET service as soon as developmental work on them is complete. A healthy tension between service and development works to keep PROPHET's maturation on course with that of the mainstream of laboratory and clinical investigation. The evaluation and refinement of successive service versions of PROPHET is a principal thrust of the CBIH Program.

The continuing design, development, and operation of so complex a research resource as the PROPHET System is a formidable task--one whose nature and scope almost certainly are beyond the means of any single institution, public or private. The task demands familiarity with both the biological and physical sciences; it involves interaction with biomedical investigators across the spectrum from molecular biology to patient care; it entails the coordination of extensive engineering development; and it requires the provision of high quality computer services and associated technical assistance on a national scale. Sustained,

intensive collaboration among academe, the private sector, and the Federal Government is the only approach offering a high likelihood of success. The PROPHET project is just such a national collaborative effort.

After two years of preliminary design, two years of prototype implementation, and four years of continuing evaluation and refinement in a full service environment, the PROPHET System now is well established as a research resource. It reflects the combined talents and coordinated energies of a Software Development Contractor, a Facility Management Contractor, and a DHEW-chartered Advisory Committee (see Tables I and II). It serves over 100 users distributed among 12 institutions in 9 states (see Table III). While many needs and opportunities for further development of the resource exist, PROPHET already is the most nearly comprehensive array of computer tools for the study of chemical/biological interrelationships ever to be integrated into a single system and made available as a service to the biomedical community in national competition.

Substantial documentation exists regarding PROPHET and its research uses. The features of the System are explained in detail in several manuals (1, 2). The principal characteristics of PROPHET's architecture have been reviewed from several perspectives (3,4,5). There are accounts of specific research projects involving PROPHET (6,7,8,9), as well as a discussion of issues associated with the management and administration of the resource (10) and a bibliography comprised of reports of research results toward which PROPHET contributed (11).

RESEARCH APPLICATIONS OF THE PROPHET SYSTEM

A. Tabulation of Research Projects Active in Fiscal Year 1976

The research uses of PROPHET are many and varied, reflecting the heterogeneity of studies involving chemical/biological interactions. PROPHET users range from molecular biologists and quantum pharmacologists concerned with the fine details of biomolecular mechanisms to epidemiologists and social scientists dealing with the study of disease in population groups. The applications of the System range from (a) management of empirical data gathered in the laboratory and clinic through (b) statistical analysis and pharmacokinetic modelling to (c) the construction and manipulation of molecular models.

Tables IV.A - IV.K summarize the research uses of the PROPHET System during Fiscal Year 1976. In general, each table deals with one user installation. The principal exception is Table IV.F which involves the collaboration of investigators at three sites.

The format of the tables hopefully is self-explanatory. For the most part, the individuals identified are affiliated with the institution housing the PROPHET terminal. There are a few exceptions (e.g., scientists located at neighboring institutions), but these other institutions are not included explicitly in the interest of keeping the tabulations simple. The use of the phrase "same as number" under the heading "sponsor(s)" signifies not only the same funding source but also the same grant or contract award.

B. Intraagency Agreement: Tabulation and Analysis of Immunoglobulin Sequence Data

As described in detail in the CBIH Program's Annual Report for Fiscal Year 1975, the PROPHET System is used heavily in research on the molecular basis of antibody specificity. This work under the direction of Dr. E.A. Kabat now is sponsored directly by the Division of Research Resources and three other NIH components: the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). This agreement not only makes possible the pursuit of an important line of scientific inquiry but also establishes an important administrative paradigm for the broad based support of PROPHET System activities.

Work under the intraagency agreement during the past year yielded the following results.

1. The computer data base of amino acid sequences of the variable regions of immunoglobulin light and heavy chains was expanded to include many newly published sequences. This data base, which now contains essentially every partial or complete immunoglobulin variable region sequence which has appeared in the refereed scientific literature, was rigorously verified in most instances by having each sequence checked by the scientist who had originally published it. Efforts to produce copies of this unique compilation in easy-to-use hard copy form now are in the final stages, and the resulting computer-generated document should be ready for broad distribution by summer. It will contain not only the primary aligned sequence data but also variability plots of selected subsets of the sequence collection.

2. Computer-assisted analyses of the immunoglobulin variable region sequences have revealed new insights about the structural bases of antibody specificity and have resulted in two publications. First, a λII (Vi1) and a λV (Mcg) Bence-Jones protein were found to have identical first complementarity-determining segments 14 residues long despite 21 amino acid differences in their variable regions (12). If a different structural gene is responsible for each light chain subgroup, the findings tend to support the concept that the amino acids which comprise the hypervariable or complementarity-determining segments arise as a result of an episomal insertion mechanism.

   Second, the computer has been used to select greater than random occurrences of pairs of residues in complementarity-determining segments; and it was found that the sequence phenylalanine-tyrosine-methionine-glutamic acid occurred only in the 6 phosphocholine-binding myeloma proteins in the data bank (13). This sequence of four amino acids occurred only at positions 32-35 of the heavy chain and nowhere else either in the remainder of the immunoglobulin data base or in the computer version of The Atlas of Protein Sequence and Structure (14). These results suggest that characteristic amino acid sequences in the complementarity-determining segments of immunoglobulin variable regions may be uniquely associated with certain antibody combining sites.

3. Previously reported methods (15) for predicting the secondary structural characteristics of proteins from sequence data were refined further and, along with a variety of other methods, were applied to immunoglobulins of known three-dimensional structure. In general, α helical regions were predicted with reasonable success, but β-sheet predictions showed only marginally good agreement with X-ray data. The comparative effectiveness of the various predictive methods are documented in a manuscript which now is in the final stages of preparation.

C. An Application of The PROPHET System in The Study of Histamine Structure/Activity Relationships

While Tables IV.A - IV.K give one some feeling as to the scope of PROPHET System uses, they necessarily are too brief to impart much about any one individual research project in terms of its significance, its intellectual excitement, or the ways in which PROPHET facilitates its progress. Accordingly, this section is devoted to a discussion in some detail of one investigation which made extensive use of PROPHET during Fiscal Year 1976. Perhaps this illustration will help the reader to appreciate how PROPHET functions as a national research resource.

1. The Problem

The research discussed below is representative of a group of interrelated projects being conducted with the assistance of the PROPHET System within the Department of Pharmacology, Mount Sinai School of Medicine. The subject is histamine, its agonists and antagonists, and the mechanism by which these molecules affect histamine receptors throughout the body to produce a wide variety of biological effects. The studies involve collaborative efforts among several faculty members--notably Drs. J.P. Green, C.L. Johnson, H. Weinstein, S. Kang, and D. Chou.

Histamine is a ubiquitous chemical substance, occurring naturally in essentially all animal and vegetable tissues. It is known to be a powerful dilator of capillaries, a stimulator of gastric secretion, and an effector of increased heart rate and strength of heart muscle contraction. It is generally thought to play a central role in allergic reactions. Many different antihistamine compounds are in routine use as therapeutic agents for the common cold, allergies, and other maladies, and many more are under active development in academic and commercial laboratories.

Within this last decade, convincing evidence has emerged that there is more than one kind of histamine receptor (16). For example, the well known antihistamine agent pyrilamine (mepyramine) has been shown to have no effect on histamine-mediated secretion of gastric acid or on the heart rate. Other studies with synthetic histamine antagonists have served to distinguish pyrilamine-sensitive (H1) receptors from pyrilamine-insensitive (H2) receptors and have led to the introduction of burimamide and related compounds, a group of synthetic H2 receptor antagonists which have considerable promise as agents for the treatment of duodenal ulcer. The emergence of more than one kind of histamine receptor is analogous in many ways to the earlier demonstration that two kinds of adrenergic receptors mediate the biological effects of catecholamines.

The investigators at Mount Sinai are concerned, among other things, with elucidating the detailed mechanism by which histamine influences the heart rate (chronotropic effects) and the strength of cardiac muscle contraction (inotropic effects). Histamine is thought to affect H2 receptors in the heart, stimulating adenylate cyclase which, in turn, catalyzes the formation of cyclic-adenosine monophosphate (cyclic AMP) from the energy rich adenosine triphosphate (ATP). Working through the cyclic AMP system as it apparently does, histamine thus exhibits a mode of action known to be associated with many different hormones and target organs. The experiments at Mount Sinai are designed to explain histamine-mediated effects on the cardiac adenylate cyclase system in terms of the structural and electronic properties of the molecules involved and thereby lay a firm theoretical base for the design of improved histamine agonists and antagonists.

2. Measurement of Dose/Response Relationships

The dose/response relationships of histamine and a variety of related compounds are being measured on the cardiac adenylate cyclase system. For each substance tested, a number of different doses are applied to a broken cell preparation made from guinea pig cardiac muscle. A dual isotope technique is employed--P^{32}ATP to follow the rate of formation of P^{32}/cyclic AMP and H^3/cyclic AMP to monitor the yield of the separation procedure. This experimental paradigm gives a measure of the relative potency of the various histamine agonists and antagonists and sets the stage for comparative analysis of their biological effects.

The data resulting from each experiment are stored within the computer as a collection of PROPHET tables--one table per experiment. These tables all have the same structure, a data organization especially defined by the Mount Sinai investigators (using PROPHET's repertoire of TABLE-handling commands) to reflect the special requirements of their study. Each column of the standard table corresponds to a specific class of critical observations or derived values--i.e., the times associated with the various experimental maneuvers with the preparation; the raw scintillation counter values for P^{32}/cyclic AMP and H^3/cyclic AMP; the percent recovery of cyclic AMP; the counts per minute recorded from radioactively labelled cyclic AMP; the total number of picomoles of cyclic-AMP produced; the number of picomoles of cyclic AMP produced per minute per milligram of tissue; and the results of tests of significance comparing the observed rates of cyclic AMP production in the presence of hormone with the basal rate. Each row of the standard table contains the observed and derived data associated with one particular experimental maneuver on the preparation--e.g., the addition to the medium of 0.01 millimolar histamine or 0.1 millimolar burimamide. A number of small programs in the PL/PROPHET language operate on the raw data recorded in one part of the standard table to produce the various derived values and insert them into appropriate locations in other parts of the standard table.

Once the data for any given experiment are recorded within a PROPHET table, they are readily available for convenient interactive visual inspection on the graphic display terminal in either tabular or graphic form; they also can be easily subjected to various mathematical manipulations (e.g., see below). Moreover, these data tables can be stored indefinitely in the System

either "on-line" or on a special archival storage structure) and retrieved individually or in combinations by their user-assigned names at a later time--such as when the user wishes to test a new hypothesis. The opportunity PROPHET affords its users to have their experimental data readily available to them in an organized, machine manipulable form does much to insure that no important idea is allowed to go unexamined because of the tedium associated with manual data-handling.

3. Analyses of Relative Potencies

Using the experimental data recorded in PROPHET tables, dose/response curves are generated in semilog form for the various substances being studied. These curves generally have a sigmoid shape and, if the substances work through the same mechanism, exhibit parallel slopes. If one compound has a curve located to the right of the curve for a second compound, the first compound in all likelihood has a lower affinity for the receptor than the second. If the dose/response curve for a given substance shifts to the right when an inhibitor is added to the medium, the magnitude of the shift provides a measure of the potency of the inhibitor.

In order to make effective use of dose/response curves in assessing relative potencies of various substances on the cardiac adenylate cyclase preparation, one needs to begin with a good objective fit of some functional form to the experimental data. The Mount Sinai investigators use the following logistic function

$$r = \frac{M \cdot D^P}{K^P + D^P}$$

where r is the magnitude of the response (in this case the rate of cyclic AMP formation); M is the maximum response; K is the dissociation constant; D is the concentration of the agonist or antagonist; and P is an arbitrary constant. This function is capable of producing a family of sigmoid curves that summarize well the kinds of experimental data that are involved. Because the function is nonlinear, an iterative curve fitting procedure is required--either a special program written by Dr. Johnson of Mount Sinai or the MLAB Program developed at NIH's Division of Computer Research and Technology and now featured as part of PROPHET's set of data analysis tools.

Once the dose/response curves have been computed, they may be stored in the computer indefinitely and, as needed, graphed singly or in combinations to facilitate comparison; this portion of the work makes use of PROPHET's comprehensive collection of GRAPH-handling commands and functions. Moreover, one can invoke statistical calculations such as a variance ratio test (the F statistic) and a range test to determine whether or not the slopes differ significantly from one another. When slopes are essentially equal on these dose/response curves, the relative locations of points of equal response give a clear indication of the comparative potencies of the agents involved. Also, the computed value of the dissociation constant (K) can be used in determining whether the same receptor is being affected, either when one is assessing

different substances in the same tissue preparation or comparing results of the same substance on different tissue preparations (e.g., cardiac muscle vs. ileum). The availability of the PROPHET System at Mount Sinai makes possible a rigorous, reproducible, and efficient method for the calculation and analysis of these dose/response curves. The alternative to using a research tool like PROPHET is to perform much less satisfactory "eyeball" curve fitting; to undertake tedious, error-prone, manual calculations and graph-making; or to use noninteractive batch computer processing.

4. A Mechanistic Model for the Receptor Action of Histamine

Rigorous analyses of dose/response relationships are valuable to pharmacologists in their own right, but they are especially interesting when coupled with attempts to model the detailed mechanism of action of the agents in question. The histamine/cardiac adenylate cyclase system presents such an opportunity, and related research by the Mount Sinai investigators takes advantage of it as described below (17,18,19).

The approach to mechanistic modelling is based on the fact that the histamine molecule exhibits tautomerism--i.e., it exists as a mixture of two different molecular arrangements which are mutually interconvertible under normal conditions and in dynamic equilibrium. Considerable evidence indicates that in its electrically neutral form the histamine molecule occurs mainly as the N(1)H tautomer (Figure 1a) whereas when its side chain nitrogen is protonated (i.e., acquires an extra hydrogen and hence a positive charge) the N(3)H tautomer is predominant (Figure 1b). This preference for one tautomer or the other depending upon the state of the side chain nitrogen seems to be independent of the three dimensional shape assumed by the side chain.

Several years ago, comparative analyses of the chemical structures of histamine analogs led to the suggestion that tautomerism might play a role in the mechanism of action of histamine agonists, especially on the H2 receptor (20). Moreover, recent data suggest that a molecule's ability to be an effective H2 receptor-agonist may be determined by whether it is capable of undergoing the 1,3-tautomeric transformation that is characteristic of histamine (21). The Mount Sinai group is attempting to determine precisely how a tautomeric shift might be involved in histamine/receptor interactions.

This work relies heavily on the methods of quantum chemistry, especially ab initio molecular orbital calculations. Using a large-scale general-purpose computer at the City University of New York, the Mount Sinai investigators determined the electron density distribution for the histamine molecule in (a) its electrically neutral form, (b) its cationic form (i.e., with the side chain nitrogen protonated), and (c) under conditions of a simulated interaction of the protonated side chain nitrogen of the cationic form with a negatively charged group (a hydroxyl group)--such as might be found in a receptor site. Further, they examined the redistribution of electronic charge that accompanies deprotonation of the side chain and compared it with the redistribution that occurs when there is a simulated interaction of the "cationic head" of histamine with a negatively charged site.

They accomplished the above as follows. First, they transferred the electron density results determined with the large-scale, general-purpose computer to files in the PROPHET computer. Then, using PROPHET's GRAPH-handling capabilities, they generated (a) density maps (with contour lines joining points of equal electron density), (b) density difference maps (with contour lines joining points of equal differences in density between the maps of two different molecules), and (c) electrostatic potential maps (with contour lines connecting points of equal energy). These various types of graphic display of the results of the quantum chemical calculations were made even more useful by some special-purpose programming within PROPHET by Dr. Johnson; he developed a procedure to generate a three-dimensional stick figure model of the histamine molecule and visually embed it within the maps described above. This facilitated significantly the interpretation of the quantum chemical results in terms of chemical reactivity and biological action mechanisms.

Using the PROPHET System for interactive study of the density difference maps and other outputs from the quantum chemical calculations, the Mount Sinai investigators found that the charge redistribution within the cationic form of histamine molecule accompanying its simulated approach to a negatively charged site is the same as the charge redistribution that occurs following deprotonation. Moreover, as this redistribution of electron density occurs, the N(1) position on the imidazole ring becomes more reactive and the N(3) position becomes less reactive; and these changes in reactivity parallel the shift in predominant tautomeric form that is found both experimentally and theoretically.

The above findings lead the Mount Sinai group to postulate that the interaction of histamine with the H2-receptor induces a "charge relay system" and thereby triggers the biological response. In brief, as the protonated form of histamine approaches a negatively charged receptor site, the electronic status of the imidazole ring nitrogens is thought to change such that the N(1) position attracts a proton and the N(3) position gives up a proton. If these two protons come from and go to sites on the receptor molecule (e.g., protein side chains), the net result of the interaction of histamine with the receptor would be to effect a proton transfer between fairly widely separated portions of the receptor molecule. This proton transfer in turn would alter in all likelihood the electronic state of the receptor, leading possibly to a conformational change and subsequent biochemical events that eventually manifest themselves as a biological response.

Like most findings at the frontiers of science, the work described above raises as many questions as it answers and sets the stage for many exciting follow-up studies. It seems indisputable, moreover, that this sort of theoretically oriented approach to understanding structure/activity relationships prefigures the course in which the science of pharmacology is destined to evolve. This evolution obviously cannot occur in the absence of highly motivated, talented investigators such as the Mount Sinai group who are challenged by the promise of these methodologies and the relevance of this research to improved human health. And the pace of this evolution is not likely to be satisfying unless the maturation of this discipline proceeds hand-in-hand with the use and further refinement of advanced

computer tools such as the PROPHET System. It is through support of and interaction with studies of this sort that the CBIH Program is working to fulfill its mission.

NEW PROPHET USER GROUPS

Three research groups joined the PROPHET System user network during the past year. They are located at the Stanford Research Institute, the Cleveland Clinic, and the University of California at San Francisco (see Tables III and IV). Each group has found PROPHET to be a valuable adjunct to its investigative efforts and in turn has provided the PROPHET developers with some challenging new contexts in which to evaluate and refine the System's capabilities. The research interests of these new user groups are summarized below.

1. The investigators in the Life Sciences Division of Stanford Research Institute are engaged in the study of a wide variety of topics in the general area of medicinal chemistry. Examples are research on the inhibition of the enzyme histadine carboxylase, the development of male and female chemical contraceptive agents, and the synthesis and DNA binding of actinomycin analogs. The full array of PROPHET capabilities are utilized in this work, especially the commands and procedures for handling molecular structure descriptions. Moreover, the group has contributed important guidance for the development of new PROPHET features such as new topological descriptions for molecular structure data.

2. At the Cleveland Clinic, the research focus is on the structure and function of the small polypeptide angiotensin II and its analogs. Angiotensin II is known to play an important role in the regulation of blood pressure in health and disease. Through structure/activity analyses of a variety of small polypeptides related to angiotensin II, the scientists at the Cleveland Clinic are seeking not only to understand the mechanism of action of these substances but also to design therapeutic agents which can be used clinically in combatting chronic hypertension and other human cardiovascular disorders. The PROPHET System facilitates this work by providing powerful yet easy-to-use capabilities for tabulation and analysis of the wealth of chemical and biological data that exists for angiotensin II and its analogs and for the construction, manipulation, and analysis of molecular models of these polypeptides. The extent and complexity of the data available at the Cleveland Clinic are such that the use of modern computer methods is required if one wishes to test all the hypotheses about structure/activity relationships that deserve consideration.

3. The Department of Pharmaceutical Chemistry of the University of California at San Francisco carries out a heterogeneous array of studies at the forefront of modern biomedical science. Some investigators are exploring how small molecules such as drugs and hormones interact with large ones such as proteins and nucleic acids. Other investigators are employing quantum chemistry techniques to calculate electronic indices for molecules such as thyroid hormone analogs in a search for new correlates of observed biological effects. Still others are interested in the kinetics of drug distribution, metabolism, and excretion by animal and human systems and are

developing and testing mathematical models of these phenomena. These scientists need PROPHET's full repertoire of capabilities and, while they have had access to these capabilities for only a few months to date, give promise not only of using them effectively but also of stimulating the emergence of new System features of wide applicability. For example, they use the MULTI MOLECULE facility (1) to examine postulated interactions between hormones and protein receptors.

NEW AND IMPROVED PROPHET FEATURES

As in previous years, there was a substantial effort to improve the range and quality of PROPHET System capabilities during FY 1976. Part of the past year's developmental efforts was devoted, of course, to the addition of new substantive features; but much of the developmental work was devoted to improving established features in terms of operational efficiency and user flexibility.

Among the new substantive features incorporated into PROPHET within the last year were some specific aids to data analysis--a capability to create frequency distribution tables; an orderly sequence of nonparametric statistical tests; an embellishment of the graph-handling commands to allow for the generation and display of histograms; and an extension of the data type GRAPH such that computed confidence limits can be readily associated with specific data points and conveniently depicted on the graphic display screen as conventional confidence bars. These additions to PROPHET, along with its previously existing capabilities for data management and its ever growing armamentarium of biostatistical commands and procedures, offer users a rich repertoire of techniques for dealing with their laboratory and clinical research data.

In the area of molecular modelling, PROPHET's COMPUTE MODEL command was upgraded to include a special algorithm for computing three dimensional models of molecules containing rings (22). With this improvement, users interested in the detailed conformational properties of molecules such as steroids, cannabinoids, thyroid hormone analogs, and more complex entities can generate chemically plausible three dimensional representations directly from connectivity tables without necessarily employing in the computation emprirical data obtained from X-ray crystallography. This added option in model building capability extends PROPHET's molecule-handling techniques to encompass pharmaceutically relevant substances of almost arbitrary structural complexity and enhances the utility of this aspect of the System.

The substantive additions in the graph-handling and molecule-handling areas were augmented by related modifications designed to facilitate user/System interaction and/or to make more efficient use of hardware resources. For graphs, the introduction of an EDIT GRAPH command resulted in a first-order improvement in the ease with which users can exercise PROPHET's comprehensive set of tools for arraying and manipulating data in graphical form. For molecules, a specialized display subsystem was developed to show the interactions among several molecules.

Perhaps the most important contribution to user convenience and System efficiency during FY 1976 was the introduction of the "saving compiled code" feature -

a technically difficult implementation for a system such as PROPHET where the user language is rich and where more than one user job at a time is competing for memory and other hardware resources. In brief, this feature allows a user to save his/her PL/PROPHET programs from one usage session to another in their compiled ("machine language") form - i.e., the encoding in which they are directly executable by the computer. Until recently, a user could save his/her PL/PROPHET programs from session to session only as a series of English-like statements in the PL/PROPHET language ("source code"). For each usage session in which one or more of these programs were to be employed, the user had to have the source code for those programs translated ("compiled") anew into their machine language form ("object code") by a special part of the PROPHET System software (the PL/PROPHET compiler). Now the recompilation step, which can consume several minutes of computer time, will be required only when the user makes changes in a program or when a new service version of the PROPHET System software is introduced.

Some extensions to the PROPHET central computer hardware accompanied the software improvements noted above. First, the main computer memory was expanded from 192,000 to 256,000 words in order to increase the number of users who can be active simultaneously with acceptable response time. Second, the number of entry points ("ports") into the System was increased from 24 to 32 to keep pace with the addition of new user sites. Third, several disc storage drives which were declared surplus by NIH's Division of Computer Research and Technology were acquired by the CBIH Program late in FY 1976. The addition of this equipment should increase by more than 50% the "on line" file storage capacity available to PROPHET users.

Looking to the future, FY 1976 marked the beginning of a multiyear efficiency improvement effort in the area of data management that is as ambitious as some of the original PROPHET System design and implementation activities. Specifically, the PROPHET contractor staff undertook a comprehensive analysis and evaluation of the table-handling software preparatory to a major redesign and recoding of this portion of the System. Table-handling is the heart of PROPHET's data-management capability; and, after four years of user-driven evaluation and fine tuning of the original software in the context of a full service environment, there now exists the knowledge base to repackage and extend PROPHET's approach to table handling in ways that will be much less demanding of hardware resources and much more flexible in terms of man/machine interaction. The results of this ongoing effort should begin to make their impact during the coming year.

Activities such as the above are a vital part of the CBIH Program, for if a research resource is to be successful its repertoire of tools and services must grow and change in concert with the needs and expectations of its users. The special attention paid during the past year to efficiency and flexibility indicates that the resource has matured to a point where there is broad general agreement not only as to what its basic features should be but also as to what performance parameters are most important. This is not to say that PROPHET will not continue to expand its range of capabilities in response to perceived user needs. But it does say that the resource has passed beyond adolescence and that its developers and users now have a good detailed

- understanding of what data management and molecular modelling tools are important to the study of chemical/biological interactions.

PROGRAM PLANNING

Formal program planning is a sine qua non in collaborative endeavors such as the PROPHET Project. The planning process helps program participants and advisors identify a wide variety of possible objectives (some of which might otherwise be overlooked) and leads to the establishment of specific program priorities. The very act of making objectives and priorities explicit in written form works to mobilize and focus the talents and energies of everyone involved. And the subsequent broad distribution of the resulting program planning documents does much to insure good communication among program participants and to promote highly effective application of fiscal and human resources toward common ends.

During the past year, the CBIH Program staff aided by contractor personnel, PROPHET users, and advisors--prepared a Management Plan (11) for the period Fiscal Years 1976-1980. This Management Plan lists five specific objectives:

- o increase the number of PROPHET user groups by a factor of three;
- o refine and extend PROPHET's repertoire of information-handling tools;
- o promote the emergence of special public data bases within PROPHET;
- o increase user cost participation in the PROPHET project by a factor of two; and
- o promote the deployment of PROPHET software at other computer facilities

Associated with this set of objectives is a detailed narrative giving the supporting rationale and projected costs for the full period. This Management Plan is proving invaluable not only in coordinating and directing PROPHET System activities but also in communicating about PROPHET with other Federal officials and the extramural biomedical research community.

ADMINISTRATIVE ISSUES

1. Allocation of PROPHET System Resources

As the PROPHET System matures as a research resource, it is important for Program staff and advisors to reassess from time to time the orientation of System development activities and the policies and procedures used in the allocation of services. Such a reassessment proved especially timely during the past year, given the emphasis in the Management Plan on increasing the number of PROPHET user groups. The following recommendations relevant to this topic were made by the CBIH Review Committee:

a. The PROPHET user community should continue to be comprised principally of high quality investigators working in the area of chemical/biological interaction mechanisms. Extensions to PROPHET should continue to focus principally on computer tools for this class of investigators; and CBIH Program managers should not be influenced to broaden user eligibility criteria to include other types of biomedical research even though the PROPHET System has many proven features which are applicable well beyond its mandated subject matter area. If Program staff and advisors are not continually vigilant to keep substantive boundaries clearly defined, the hardware and manpower resources of the PROPHET System quickly could be spread too thinly to be maximally effective.

b. The CBIH Program staff should undertake some special efforts to make PROPHET known more broadly within the scientific community, especially by those scientists who have not been attracted to computer use in the past but who have significant information-handling problems. Because of a backlog of "approved but not awarded" research prospectuses and the severe fiscal constraints of recent years, the CBIH Program staff has not been aggressive in soliciting new PROPHET research prospectuses; many scientists who have need for the capabilities of the PROPHET System undoubtedly are not aware that this is a national resource whose services can be applied for through a defined peer review procedure. A PROPHET exhibition at a major scientific meeting (such as the annual meeting of the Federation of American Societies for Experimental Biology) should be considered seriously.

   In response to this recommendation, a PROPHET exhibition was held at the 1976 meeting of the Federation of American Societies for Experimental Biology (FASEB) in Anaheim, California during the period April 12-16. A module of space in the institutional exhibit area was rented and fitted out with (a) a number of poster papers illustrating the work of selected PROPHET users; (b) a Tektronix graphic display terminal and appropriate telephone modems for on-line demonstrations of PROPHET; (c) a table-top projection system for showing the PROPHET motion picture; and (d) a wide variety of of descriptive literature on the System. The exhibit was manned throughout the week by various combinations of the CBIH Program Director and staff of Bolt Beranek and Newman Inc. The exhibit achieved its objective of making the PROPHET concept more broadly known within the mainstream of the biomedical research community. Analogous exhibits seem appropriate for some smaller scale scientific meetings in the future.

c. The review criteria for access to the PROPHET System should be altered. The present criteria tend to favor those applicants who have expertise in the use of computers over those applicants who are computer-naive. This weighting of the criteria clearly was appropriate for the formative years of the PROPHET System. But now that PROPHET is a mature research resource, it seems beneficial to "tilt" the criteria somewhat toward those scientists who have yet to realize the benefits of computer technology in their work.

In keeping with this recommendation, the Program staff revised the criteria by which PROPHET research prospectuses are to be assessed and rewrote the accompanying guidelines for prospectus preparation. The new criteria and associated weights are as follows:

Criterion	Points
o the scientific merit of the research activities described and their relevance to the objectives of the CBIH Program	40
o the likelihood that access to the PROPHET System can facilitate the offeror's research	40
o the likelihood that the offeror's uses of the PROPHET System will contribute significantly toward its further development	20

The new guidelines for prospectus preparation now are in their final stages of development and administrative review and soon will be ready for release.

2. Fire and Smoke

One event during the past year almost made the CBIH Program's plans irrelevant. On Saturday night, April 10, 1976, a major fire occurred in the building in Waltham, Massachusetts, which houses the PROPHET computer along with a number of computers belonging to First Data Corporation, the PROPHET Facility Management Contractor. The blaze apparently started in an electrical utility closet on the first floor (two stories below First Data Corporation's computer room) and quickly spread up the electrical conduit to the upper levels. Much of the equipment in the First Data Corporation room was damaged heavily by the flames. All of the equipment was blanketed with thick, sooty smoke from the burning cabling and doused with water by fire fighting crews. By the time the fire was extinguished, the operations of First Data Corporation and PROPHET had been disrupted totally, and a significant portion of the equipment and facilities had been disabled, possibly permanently.

By good fortune, the PROPHET computer equipment was located in one of the areas of the machine room furthest from the entry point of the flames; no data files or other information stored in the computer were lost and all but some minor components of the PROPHET hardware were spared irreversible damage. Within three days of the fire, temporary electric power and telecommunication lines were connected to the PROPHET machine and most of the equipment was powered up for testing. Within one week of the fire, all principal PROPHET hardware components except the swapping drums were back in operation in support of the System's nationwide user clientele. The swapping drums (peripheral storage devices which have high speed transfer rates into and out of memory and which thus make it possible for many users to run programs simultaneously) had to be removed to a separate building, dismantled, refurbished, and reinstalled before it was judged safe to turn on their power supplies and test their sensitive electromechanical components. Nevertheless, within one month after the fire, the swapping drums were running on a regular service schedule along with the rest of the PROPHET hardware.

While PROPHET services are quickly reapproaching their traditional high standards, the prognosis for the long term health of the hardware is uncertain. It is almost inevitable that the PROPHET computer will exhibit a higher rate of maintenance problems in the months immediately ahead than anything experienced heretofore. Given the complexity of modern computer equipment, some of the residual damage within the PROPHET hardware may prove sufficiently subtle to be virtually irreparable. A reexamination of the options for modernization of the PROPHET hardware therefore is high on the program planning agenda.

No account of "Black Saturday" and its aftermath would be complete without a tribute to the personnel of First Data Corporation. With much of their commercial time-sharing computer equipment damaged beyond repair and their corporate existence hanging in the balance, they were able to effect quick restoration of at least basic computer services to their principal commercial clients and to PROPHET users. Throughout this most trying period, they never failed to maintain the high standards of technical excellence and professionalism for which they have become known within the computer time-sharing service industry.

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TABLE I

CHEMICAL/BIOLOGICAL INFORMATION-HANDLING PROGRAM

CONTRACTORS

1. PROPHET SYSTEM SOFTWARE DEVELOPMENT

   Bolt Beranek and Newman Inc.
   Cambridge, Massachusetts
   Paul A. Castleman, Project Director

2. PROPHET SYSTEM FACILITY MANAGEMENT

   First Data Corporation
   Waltham, Massachusetts
   David Friesen, Project Director

3. PRINCIPAL SUBCONTRACTORS

   a. Digital Equipment Corporation
      Maynard, Massachusetts
      Manufacturer of the DEC PDP-10 Computer

   b. Tektronix, Incorporated
      Beaverton, Oregon
      Manufacturer of the 4010 Graphic Display Terminal

   c. American Telephone and Telegraph
      Telecommunication Lines and Services

TABLE II

CHEMICAL/BIOLOGICAL INFORMATION-HANDLING REVIEW COMMITTEE

MIYA, Tom S. (Chairman) (77)
Professor and Chairman
Department of Pharmacology and Toxicology
School of Pharmacy and Pharmacal Sciences
Purdue University
Lafayette, Indiana 47907

ABBOTT, Robert P. (78)
Divison Leader
Computer Research Projects Division
Computation Department
Lawrence Livermore Laboratory
Livermore, California 94550

DAVI, Sumana K. (76)
Senior Investigator
Dermatology Branch
Division of Cancer Biology and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

GRUNEWALD, Joan O. (78)
Assistant Professor
Department of Biochemistry
School of Medicine
University of Kansas
Kansas City, Kansas 66103

JACQUEZ, John A. (79)
Professor
Department of Physiology
Medical School
University of Michigan
Ann Arbor, Michigan 48104

PAUKER, Stephen G. (77)
Assistant Professor
Department of Medicine (Cardiology)
New England Medical Center Hospital
Boston, Massachusetts 02111

WOODS, Eugene F. (76)
Senior Research Pharmacologist
Department of Pharmacology
Baxter-Travenol Laboratories
6301 Lincoln Avenue
Morton Grove, Illinois 60053

Executive Secretary

RAUB, William F.
Program Director
Chemical/Biological Information-Handling Program
Division of Research Resources
National Institutes of Health
Bethesda, Maryland 20014

July 1, 1975

TABLE III

PROPHET USER GROUPS
(As of June 1976)

1. Department of Pharmacology
   School of Medicine
   University of Pittsburgh
   Pittsburgh, Pennsylvania

2. Harvard University General Clinical Research Center
   Beth Israel Hospital
   Boston, Massachusetts

3. Department of Pharmacology
   Mount Sinai School of Medicine
   New York, New York

4. Molecular Biophysics Department
   Medical Foundation of Buffalo
   Buffalo, New York

5. Research Institute on Alcoholism
   New York State Department of Mental Hygiene
   Buffalo, New York

6. Technological Institute
   Northwestern University
   Evanston, Illinois

7. Harborview Medical Center
   University of Washington
   Seattle, Washington

8. Biology Department
   Yale University
   New Haven, Connecticut

9. Cleveland Clinic Foundation
   Cleveland, Ohio

10. Life Sciences Division
    Stanford Research Institute
    Menlo Park, California

11. Department of Pharmaceutical Chemistry
    University of California
    San Francisco, California 94122

12. Division of Research Resources
    National Institutes of Health
    Bethesda, Maryland

TABLE IV

RESEARCH APPLICATIONS OF THE PROPHET SYSTEM

DURING FISCAL YEAR 1976[1/]

Table IV.A. Department of Pharmacology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

	Project	Investigator(s)	Sponsor(s)
1.	Drug interactions through hepatic depot formation	J. Anderson	Medical Alumni Assn., U. of Pittsburgh
2.	Uptake of quaternary ammonium compounds by rat liver	J. Anderson with S. Somani	--
3.	Cellular calcium Homeostasis Models	J. Anderson with A. Borle and T. Uchikawa (Physiology)	NIAMDD
4.	Uptake and metabolism of dipeptides by liver	J. Anderson S. Adibi (Medicine)	NIAMDD
5.	Uptake of propranolol by liver	J. Anderson	NHLI
6.	Study of phenotypic resistance to tetracycline	R. Connamacher	--

[1/] When listing the sponsor(s) of these research applications of the PROPHET System, abbreviations are used for all major components of NIH and ADAMHA that are represented. In addition, abbreviations are given for those programs of the Division of Research Resources that are represented. The abbreviations are as follows:

NCI	National Cancer Institute, NIH
NHLI	National Heart and Lung Institute, NIH
NIAAA	National Institute of Alcohol Abuse and Alcoholism, ADAMHA
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIAMDD	National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH
NICHD	National Institute of Child Health and Human Development, NIH
NIDA	National Institute of Drug Abuse, ADAMHA
NIGMS	National Institute of General Medical Sciences, NIH
NIMH	National Institute of Mental Health, ADAMHA
NLM	National Library of Medicine, NIH
DRR	Division of Research Resources, NIH
BRSP	Biomedical Research Support Program
GCRCP	General Clinical Research Centers Program

Table IV.A. - continued

	Project	Investigator(s)	Sponsor(s)
7.	Mechanism of iron stimulation of protein synthesis in bacteria	R. Connamacher	--
8.	Hypertension screening protocol	C. Corder with R. McDonald and T. Vagnucci (Medicine)	DRR/GCRCP
9.	Pharmacokinetics of bethanidine	C. Corder	A. H. Robins Co.,Inc.
10.	Discharge patterns in neuron populations of primate somatosensory cortex	G. Werner J. Roppolo	--
11.	Hallucinogenic drug action on the somatosensory system	J. Roppolo G. Werner H. Reitboeck	NIMH
12.	Kinetics of anticoagulant effects of warfarin in rats	L. Wingard	NIGMS
13.	Pharmacodynamics of d-tubocurarine in humans	L. Wingard with D. Cook (Anesth.)	--
14.	Kinetics of succinyl choline in neonates and children	L. Wingard	--

TABLE IV.B. Harvard University General Clinical Research Center
Beth Israel Hospital, Boston, Massachusetts

1.	The metabolic requirements for potassium excretion in the isolated perfused rat kidney	P. Silva F. H. Epstein	NIAMDD
2.	The relation between gluconeogenesis and sodium transport in the isolated perfused rat kidney	P. Silva F. H. Epstein	Same as #1
3.	Contribution of urea to the renal concentrating mechanism	P. Silva R. Swartz F. H. Epstein	Same as #1

Table IV.B. - continued

	Project	Investigator(s)	Sponsor(s)
4.	Parathyroid hormone effect on cyclic AMP, phosphate and calcium excretion in the isolated perfused rat kidney	P. Silva J. Stoff F. H. Epstein	Same as #1
5.	Calcium transport by the isolated perfused rat kidney	P. Silva A. Manitius F. H. Epstein	Same as #1
6.	Functional effects and metabolism of catecholamines in the isolated perfused rat kidney	P. Silva L. Landsberg A. Besarab F. H. Epstein	Same as #1
7.	Na-K-ATPase activity and renal respiratory rate	P. Silva F. H. Epstein	Same as #1
8.	Blood flow distribution in the isolated perfused rat kidney; effect of vasoactive drugs	P. Silva J. Rubin J. Stoff F. H. Epstein	Same as #1
9.	The energy cost of sodium reabsorption	P. Silva F. H. Epstein	Same as #1
10.	Control and mechanism of release of erythropoietin production by the isolated perfused rat kidney	P. Silva S. Robinson W. McLaurin F. H. Epstein	Same as #1
11.	Study of oral protein sparing in human subjects	G. Blackburn	MIT Center for Nutritional Research; DRR/GCRCP
12.	Analysis of nutritional status of hospitalized patients	G. Blackburn	NIGMS; NIAMDD
13.	Determination of optimal hyperalimentation infusion rates	G. Blackburn	Deaconess Hospital Nutrition Support Service; NIGMS; NIAMDD
14.	Metabolic response to severe trauma	G. Blackburn	Same as #13

Table IV.B. - continued

	Project	Investigator(s)	Sponsor(s)
15.	Effect of a protein sparing diet and brief fast on nitrogen metabolism in mildly obese subjects	G. Blackburn	Same as #13
16.	Proteolysis associated with peripheral energy fuel substrates in septic man	G. Blackburn	Same as #13
17.	Cyclic hyperalimentation: An optimal technique for preservation of visceral protein	G. Blackburn	Same as #13
18.	New concepts and treatment of cancer cachexia	G. Blackburn	Same as #13
19.	Criteria for evaluation of protein quality in hospitalized patients	G. Blackburn	Same as #13
20.	Response of QT interval of the electrocardiogram to exercise	H. Hartley	NHLI
21.	Prevalence of premature ventricular contraction induced by exercise	H. Hartley	Same as #20
22.	Effect of relaxation technique on O_2-uptake during exercise	H. Hartley	Same as #20
23.	Prevalence of premature ventricular contraction induced by exercise	H. Hartley	Same as #20
24.	The effects of exercise rehabilitation programs on the recovery after myocardial infarctions	H. Hartley	Same as #20
25.	Analysis of ultracentrifuge sedimentation rates	R. Auty M. Lanner	DRR/BRSP
26.	Effect of storage on the glutamine to glutamic acid ratio in human sera	M. Warth R. Auty M. Lanner	DRR/GCRCP

Table IV.B. - continued

	Project	Investigator(s)	Sponsor(s)
27.	Non-pharmacological approach to hypertension, anxiety, cardiac arrhythmias, headache, in post-myocardial infarction patients	H. Benson	NIMH; NHLI; Hoffman-La Roche, Inc. DRR/GCRCP; General Service Foundation of St. Paul, Minn.
28.	Evaluation of the relationship between emotional stress and ischemic heart disease with the quiz-electrocardiogram technique	F. Schiffer	NHLI
29.	Evidence for seasonal variation in 24-hour urinary creatinine excretion	B. J. Ransil D. J. Greenblatt	DRR/GCRCP
30.	Effects of sodium salicylate in acute Chagasic myocarditis in mice	F. Duncanson B. J. Ransil W. Abelmann	NHLI
31.	Dose/response effects of Gentamycin, Keflin and PAH on weight, GFR and urinary volumes	A. Sugarman R. Brown	NIAMDD
32.	Stimulation of pancreatic enzymes by Sincalide, Methacholine and Pancreozymin	G. Glazer M. Steer	King Foundation Fellowship
33.	Evaluation of a commercially available arrhythmia monitoring computer	R. Lustig S. Cohen W. Abelmann	NHLI
34.	Development of methodology for T3 RAI assay analysis	S. Ingbar B. J. Ransil	NIAMDD
35.	Methodology for comparison of experimental and theoretically derived chemical properties	B. J. Ransil	--
36.	Electron charge density basis of chemical reactivity and biological activity	B. J. Ransil	--
37.	Methodology for calculating amino acid residues	B. J. Ransil	DRR/GCRCP

Table IV.C. Department of Pharmacology, Mount Sinai School of Medicine, New York, New York

	Project	Investigator(s)	Sponsor(s)
1.	Characterization of the serotonin-LSD receptors in rat brain and rat fundus (a) Study of specific binding of tryptamine derivatives to membrane receptors and relationship to receptor activation (b) Theoretical studies of the relationship between the molecular structure of tryptamines derivatives and their biological activity	J.P.Green C.Johnson H.Weinstein S. Kang D. Chou	NIMH
2.	Histamine-sensitive cardiac adenyl cyclase	C. Johnson	Same as #1
3.	Theoretical studies on the role of tautomerism in the activation of histamine receptors. Theoretical studies in charge-relay systems in biological molecules	H.Weinstein D.Chou C.Johnson J.P.Green	Same as #1
4.	Neurophysiological studies of opiates and antagonists	J.Goldfarb	NIDA
5.	Theoretical studies on the reactivity of singlet and triplet oxygen	H.Weinstein D. Chou P. Politzer	Same as #1
6.	Kinetic analyses of product-precursor relationship in the γ-glutamyl cycle and its role in amino acid transport in the kidney and liver	C.Johnson M.Orlowski S.Wilk	NIAMDD

Table IV.D. Molecular Biophysics Department, Medical Foundation of Buffalo, Buffalo, New York

1.	Dissemination of molecular data for biomedical use	W.Duax V.Cody C.Weeks	NLM

Table IV.D. - continued

	Project	Investigator(s)	Sponsor(s)
2.	Molecular structures of steroids	W. Duax C. Weeks R. Rohrer	NCI
3.	Ultrastructure of the anti-hypertensive prostaglandins	H. Hauptman G. DeTitta	NHLI
4.	Molecular structures of thyro-active compounds	V. Cody	Julia R. and Estelle L. Foundation of Buffalo; NIAMDD
5.	Ionophores, transport and membrane structure	D. Smith	NIGMS
6.	Action of effectors upon the redox equilibrium of cyto-chrome c	G. Czerlinski	National Science Foundation

Table IV.E. Research Institute on Alcoholism, New York State Department of Mental Hygiene, Buffalo, New York

1.	Influence of lactation on water consumption in rats	E. L. Abel	Research Institute on Alcoholism
2.	Police Chief Survey	D. L. Casbeer	Division of Alcoholism New York State Dept. of Mental Hygiene
3.	Chronic effects of ethanol on the mammalian muscle spindle	D. D. Greenhouse	Same as #1
4.	Pharmacology of the mammalian muscle spindle	D. D. Greenhouse	Same as #1
5.	Mechanism of tolerance to ethanol	H. B. Greizerstein	NIAAA
6.	Demographic profile for public intoxication arrests in the City of Rochester, New York	F. J. Hooper	Same as #1
7.	Determining the prevalence of the public inebriate population utilizing arrest and conviction data for Erie County, New York as representative of an Eastern SMSA	F. J. Hooper	Same as #1

*SUNYAB-Dept. of Biochemical Pharmacology

Table IV.E. - Continued

	Project	Investigator(s)	Sponsor(s)
8.	Selected studies in nucleic acid metabolism	T. Kalman*	NCI
9.	The relationship of maternal alcohol use to intrauterine growth	M. Russell	Same as #1
10.	Intrauterine growth patterns and the incidence of congenital malformations in Upper New York State (1968-1973)	M. Russell	Same as #1
11.	Drinking patterns and alcohol-related problems in sophomore medical students	M. Russell	Same as #1
12.	Comparison of the disposition of ^{3}H-Tetrahydrocannabinol and ^{14}C-tetrahydrocannabinol in the rat	A. J. Siemens	NIDA; Same as #1
13.	Metabolic interactions of tetrahydrocannabinol and amphetamine	A. J. Siemens	Same as #12
14.	Metabolic interactions of tetrahydrocannabinol and ethanol	A. J. Siemens	Same as #12
15.	The effect of ethanol on pyridine nucleotide biosynthesis	A. J. Siemens	Same as #1
16.	Differential effects of pentobarbital and ethanol in mice	A. J. Siemens A. W. K. Chan	NIAAA: Same as #1
17.	Barbiturate dependence and neurotransmitter turnover	D. Waters*	Pharmaceutical Manufacturers Assn. Fndn.
18.	Central depressant-induced motor activity	D. Waters	SUNY Research Fndn.
19.	Barbiturate reversed-tolerance in the CNS	D. Waters	SUNY Buffalo
20.	Ethanol as a discriminative stimulus	J. L. York	Same as #1

*SUNYAB-Dept. of Biochemical Pharmacology

Table IV.F. Technological Institute, Northwestern University, Evanston, Illinois; Bolt Beranek and Newman Inc., Cambridge, Massachusetts; and National Institutes of Health, Bethesda, Maryland

	Project	Investigator(s)	Sponsor(s)
1.	Prediction of polypeptide conformation	E. Kabat T. Wu H. Bilofsky	NCI; NIAID; NIAMDD: NIGMS; National Science Foundation
2.	Tabulation and analysis of immunoglobulin sequence data	E. Kabat T. Wu H. Bilofsky	Same as #1

Table IV.G. Biology Department, Yale University, New Haven, Connecticut

1.	Growth control by membrane matrix matching lipids	B. Stowe M. Dotts	NIAMDD

Table IV.H. Harborview Medical Center, University of Washington, Seattle, Washington

1.	Hematologic and circulatory changes in the initial response to thermal injury	P. W. Curreri D. Manwaring	NIGMS
2.	Oxygen consumption in the hypermetabolic burn animal	P. W. Curreri S. Goehle	Same as #1
3.	Transmembrane potential studies in the hypermetabolic burn animal	P. W. Curreri E. Lieberman	Same as #1
4.	Burn data, miscellaneous	P. W. Curreri K. Orgain L. Montano	Same as #1
5.	Pulmonary response to thermal injury	P. W. Curreri J. Horovitz	Same as #1
6.	Leukocyte function in burn patients	P. W. Curreri L. Altman S. Klebanoff	Same as #1
7.	Hemostasis in burn patients	L. A. Harker T. Simon	NHLI
8.	Pharmacokinetics of heparin	L. A. Harker T. Simon	Same as #7
9.	Hyperlipidemia and atherosclerosis	L. A. Harker R. Ross	NHLI

Table IV.H. - continued

	Project	Investigator(s)	Sponsor(s)
10.	Platelet and fibrinogen survival in coronary atherosclerosis	L. A. Harker J. Ritchie	Same as #9
11.	Homocystine-induced atherosclerosis	L. A. Harker S. Slichter R. Ross C. Scott	Same as #9
12.	Blood cell size in health and disease	W. E. von Behrens	NHLI
13.	Diabetes Registry	J. P. Palmer	NIAMDD
14.	Coronary primary prevention trial, Lipid Research Clinic	J. A. Bowlin Other dietary staff	NHLI
15.	Lecithin Study	J. A. Bowlin	Same as #14
16.	Thyroid hormone metabolism in cold-exposed baboons	W. L. Green C. C. Gale	NIAMDD
17.	Thyroid hormone metabolism in pregnant women	W. L. Green	Same as #16
18.	Thyroid function in patients on home hemodialysis	W. L. Green J. Brunzell	Same as #16
19.	Fuel physiology, primate studies	C. J. Goodner D. J. Koerker	NIAMDD
20.	Human obesity	C. J. Goodner E. W. Chideckel	Same as #19

Table IV.I. Life Sciences Division, Stanford Research Institute, Menlo Park, California

1.	Chemical inhibitors of histidine decarboxylase	H. Johnson J. DeGraw	NIAMDD
2.	Synthesis and evaluation of nonaddicting analgesics	J. DeGraw H. Johnson	NIDA
3.	Development of mosquito repellents having increased protection time in man	W. A. Skinner H. Johnson	U.S. Army Medical Res. and Development Command

Table IV.I. - continued

	Project	Investigator(s)	Sponsor(s)
4.	Chemical contraceptives for the male and female	M. Tanabe	NICHD
5.	Methods of structure-activity analysis (QSAR)	H. Johnson M. Cory	DRR/BRSP
6.	QSAR of mutagenicity and carcinogenicity	H. Johnson M. Cory	Same as #5
7.	Novel actinomycin analogs: synthesis and DNA binding	K. Kuhlmann C. Mosher	NCI
8.	19F NMR Study of binding of drugs to DNA	K. Kuhlmann	Same as #7
9.	Synthesis of complement inhibitors	M. Cory	Same as #7
10.	Synthesis of antischistosomal chemotherapeutic agents	M. Cory	Same as #3
11.	Studies of drug interaction with DNA - Inhibition of DNA and RNA synthesis in L1210 leukemia cells	M. Cory D. W. Henry D. Taylor	Same as #7
12.	Determination of ΔT_m of drugs bound to DNA	M. Cory D. W. Henry C. Mosher N. Charbeneau K. Kuhlmann	Same as #7

Table IV.J. Research Division, Cleveland Clinic Foundation, Cleveland, Ohio

1.	Structure/activity relations of angiotensin analogs	P. A. Khairallah R. R. Smeby M. C. Khosla	NHLI; American Heart Assn., Northeast Ohio Affiliate
2.	Studies on angiotensin receptor sites	P. A. Khairallah F. F. Moore M. M. Hall	Same as #1
3.	Correlation of angiotensin conformation and biological activity	R. R. Smeby	Same as #1
4.	Studies on phospholipase A_2 kinetics	R. R. Smeby	Same as #1
5.	Studies on distribution of renal blood flow by xenon washout	N. T. Stowe J. Emma	Same as #1

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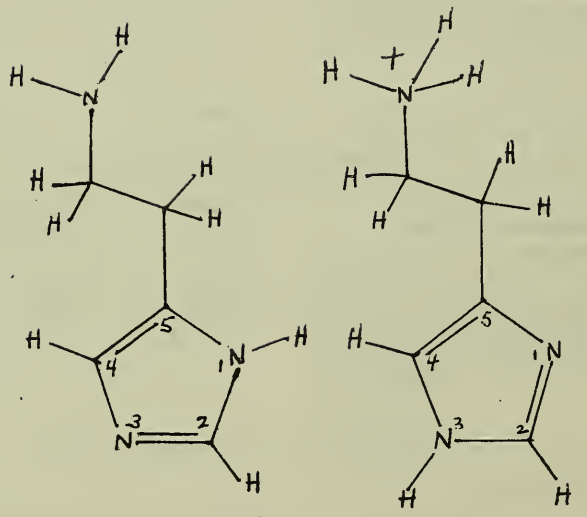
Table IV.K. Department of Pharmaceutical Chemistry, University of California, San Francisco, California

	Project	Investigator(s)	Sponsor(s)
1.	Relation of steric, electronic and hydrophobic bonding properties of steroid substituents to their biological action	M. E. Wolff	NIAMDD
2.	Pharmacokinetic data tabulation, pharmacokinetic analysis, membrane transport studies	L. Z. Benet	NIGMS
3.	Stereochemical and conformational parameters involved in the binding between phenothiazines and biological macromolecules	J. C. Craig	NIMH
4.	Solution kinetics of the tetracycline antibiotics; *in vivo* and *in vitro* metabolism of chlordiazepoxide	B. A. Hoener	--
5.	Structure of enzyme-substrate complexes elucidated by NMR relaxation phenomena	T. L. James	National Science Foundation
6.	Comparison of structural features with biological activities at all levels of biological organization of analogs of thyroid and peptide hormones	E. C. Jorgensen	NIAMDD
7.	Electronic structure theory applied to molecular structure and intermolecular interactions	P. A. Kollman	NIGMS
8.	Protein structure and protein binding of small molecules	I. D. Kuntz	NIGMS
9.	Pharmacokinetic and pharmacodynamic studies of brain tumor chemotherapeutic agents	V. A. Levin	NCI
10.	Nonlinear pharmacokinetics, competitive inhibition, dialysis and drug-protein binding studies	T. N. Tozer	--

Figure 1: Tautomeric Forms of Histamine



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Fiscal Year 1976
Annual Report
General Clinical Research Centers Program
Division of Research Resources

Goals of the Program

In 1959, the Congress expressed the view that the Nation should receive the benefits of basic research as rapidly as possible. Passage of P.L. 86-798 established the legislative basis for the General Clinical Research Centers (GCRC) Program and, in 1960, the Congress appropriated $3 million for its establishment. The GCRCs were designed as loci for clinical investigation; they were created to supplement ongoing medical research in universities and hospitals.

The GCRC Program of DRR has evolved in response to the need for specialized facilities and trained personnel that is required for high-quality clinical research. The fundamental study of human physiology and disease with its broad implications for the maintenance and restoration of health requires an optimal environment for human study. Repeated attempts to perform high-quality clinical investigation in beds scattered throughout a general hospital environment have proven unsatisfactory. Furthermore, a single general research unit would seem to meet more effectively and economically the needs of many investigators studying a variety of disease problems in a most effective and economic fashion.

The primary goal of DRR's GCRC Program is the establishment of a resource for clinical investigation to:

- Increase the knowledge of human physiology and pathophysiology by the investigation of the epidemiology, etiology, progression, prevention, control, and cure of human disease by studies in man;

- Provide an optimal setting for controlled studies by clinical investigators supported through NIH and other research support programs;

- Encourage and foster disciplinary interaction;

- Contribute to the maintenance of a national core of qualified clinical investigators, and

- Develop technological and therapeutic advances in the expeditious translation of basic biological knowledge into effective patient care.

A GCRC is defined as "a distinct organizational and physical entity providing a continuing resource for clinical research efforts, including the necessary laboratory and supporting services." Specifically, a GCRC is a resource

to a medical institution permitting quality clinical investigation. The research conducted in the GCRC derives its support from various Institutes of the NIH as well as from numerous foundations and philanthropic organizations. Funds for the GCRC Program are intended primarily for the establishment and maintenance of the separate discrete units in which clinical research is to be done.

A GCRC consists of four to thirty beds, the average being ten. The average GCRC contains ten beds, treatment rooms, a core laboratory, diet kitchen, patients' lounge, nurses' station, a conference room, and outpatient space. Typically, a center supports the equivalent of 1.4 medical directors, each with an average of $80,000 annually of independent grant support, 12 nurses, 3 dietary specialists, 2.0 lab technicians, and 1.2 administrative support positions. Over 80% of the patients admitted to the center are admitted exclusively for study purposes and are therefore not required to pay for any portion of their stay. Approximately 20% of the patients require hospitalization for diagnosis or treatment and these patients are billed for this part of their stay. In recognition of the special requirements for research in children, 123 of the currently active 779 beds are on pediatric wards or in children's hospitals. Four beds are dedicated to the study of maternal and child problems surrounding delivery and six are dedicated to research in premature infants. Seventy of the currently active centers make pediatric admissions on a regular basis.

Within the GCRCs, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for the continued development of competent investigators and improved medical care. An additional benefit of these GCRCs are the opportunities for future medical practitioners to develop knowledge which facilitates critical evaluation of new medical discoveries with which they will be confronted in their careers. In addition, the GCRCs assist in the training of large numbers of paramedical personnel.

Information concerning the research done in the GCRCs is disseminated to the medical community in a variety of ways. For example, in fiscal year 1973, there was a total of 2,360 publications and 1,175 abstracts (see Table I) which appeared in scientific books or journals.

Table I

Center Publications

Year	Publications	Abstracts
1969	2,077	931
1970	2,341	996
1971	2,229[1/]	991
1972	2,462[2/]	994
1973	2,360[3/]	1,175

1/ includes 246 publications involving outpatients
2/ includes 411 publications involving outpatients
3/ includes 549 publications involving outpatients

Scientific Review

The initial scientific and technical merit review of center applications is carried out by the GCRC 18-member Committee composed of specialists in clinical research. Each application is site visited by two or three Committee members supplemented by 4-6 ad hoc consultants. Each project using or proposing to use the center is reviewed for scientific merit and need for center resources such as beds, specialized nursing services, and dietary resources. The GCRC review is supplemented by a review of priorities assigned to investigators using the center by other study sections in arriving at an overall level of resource support (i.e., beds, nurses, space, outpatient support, etc.). In a recent two-year period, sixty-eight site visits were conducted using 322 ad hoc consultants. The GCRC Committee, in addition to performing scientific review, acts as a major advisory body for the program in advising on program priorities. Recommendations are made to the National Advisory Research Resources Council.

Fiscal Summary

The GCRC Program grew at an almost constant rate between 1960 and 1967. In the past few years, however, rising costs and fiscal constraints have prevented expansion and have limited support to fewer centers and for a decreasing number of beds. GCRCs exist in teaching hospitals affiliated with two-thirds of the medical schools in this Nation. However, there are many such institutions which do not have a center despite their great potential. Table II depicts the program history since 1968. The Program has operated effectively despite sharp inflationary rises and only modest budget increases. This has been accomplished through a number of adjustments, such as termination of a number of CRCs, reducing the number of beds supported, savings realized through new costing procedures, the development of a service patient policy, and the support of research done on an outpatient rather than an inpatient basis.

Despite budgetary constraints, the Program continues to support the best available resources for clinical research. More than half of all hospital beds in the Nation, specialized for research on humans, is supported by this Program.

During 1967-75, redistribution of beds and GCRC occurred within the Program. In 1967, 1,137 beds were approved in 91 centers. In subsequent scientific reviews, 24 centers with 213 beds were disapproved and NIH support was terminated or they were combined with other centers. On the basis of limited scientific productivity, an additional 226 beds in 46 centers were eliminated with corresponding staff reductions. During this eight-year period, 12 new centers and 6 centers which resubmitted successful applications for a total of 170 beds were funded. In addition, six of the centers given two-year renewals worked to revise their program to compete successfully with programs of high scientific merit. The net result has been a substantial improvement in the overall scientific quality of the program. The funded beds now correspond closely with the bed needs of investigators holding NIH-sponsored grants and contracts. Despite changes, rising costs have outstripped available funds. This differential has been met in part through appropriate

Table II

GCRC Program, FY 1968-1975

Fiscal Year	Medical Schools with a GCRC	Number of Centers	Funded Beds	Patient Days	Full-Time Equivalent Positions Funded	Apportionment (in thousands)
1968	62	91	1051	260,696		$ 30,443
1969	64	93	1023	245,943	2,297	35,004
1970	64	93	904	231,020	2,076	35,004
1971	56	82	881	218,716	1,885	38,004
1972	58	84	907	220,490	1,867	42,181
1973	59	83	893	204,993	1,790	41,300
1974	62	87	877	238,560	1,812	42,320
1975	61	84	823	212,831	1,749	42,619
1976	--	80*	779	184,432*	1,678	42,533
1977	--	83*				47,283*

*Estimate

collections from third party carriers and, in part, by encouraging investigators to carry out some of their activities through less expensive outpatient protocols whenever feasible.

The outpatient program initiated in 1970 has proved an effective resource for studies in chronic diseases. Conversion of bed space and redefinition of personnel requirements have taken place in 53 centers. The growth in use of outpatients for research is shown in Table III.

Table III

Summary of Outpatient Visits, 1970-1975

FY	Outpatient Visits
1970	1,175
1971	13,426
1972	24,658
1973	36,309
1974	48,845
1975	60,000 (estimate)

Program Content

The General Clinical Research Centers provide funds for patient care, space, laboratory support, nursing support, and dietary support for clinical investigation, but do not provide research funds for the investigative teams, the laboratory space, equipment, and supplies. Investigators using these centers in 1974 held an estimated $273.5 million in NIH grants and contracts, excluding support from the GRS program, distributed as shown in Table IV.

In a recent study of 18 of the 84 active centers, an increasing number of investigators using the GCRCs were found to have NIH contracts. Investigators in these 18 centers were supported by $7,789,000 in NIH contracts compared to $51,575,000 in research and program project grants. Thus, 13% of the support for these investigators using GCRCs was in the form of contracts. Many of these contracts supported clinical trials studies which more often use the outpatient facilities available in GCRCs.

Research Classification

Research conducted in the centers has covered practically the entire range of human pathophysiological disease problems. A recent classification of research conducted in the centers follows:

Table IV

Estimated Non-GCRC Support for Investigators Using GCRCs
By Institute FY 1974

	NIH/NIMH Grants and Contracts[1] Awarded to Investigators Using GCRCs	Awarded Dollars[1] (Millions)
National Institute of Allergy and Infectious Diseases	121	9.8
National Institute of Arthritis, Metabolism and Digestive Diseases	733	62.1
National Cancer Institute	318	24.9
National Institute of General Medical Sciences	149	19.7
National Institute of Child Health and Human Development	140	13.1
National Heart and Lung Institute	560	111.3
National Institute of Neurological and Communicative Disorders and Stroke	112	19.7
National Institute of Mental Health	70	6.6
Other	42	6.3
TOTAL	2245	273.5

[1] These numbers are based on a representative sampling of 18 GCRCs and prorated to the total of 84 centers active in FY 1974. Specific deletions have been made for certain centers supported by NCI programs, which reflect minimal GCRC use.

In addition, investigators reported 605 sources of nonfederal support from foundations and industry.

Table V

Research Categories of Studies on
General Clinical Research Centers
According to Pathophysiological Code
(2800 projects, 1973 annual reports)

Metabolism		38%
Carbohydrate	6%	
Lipid	6%	
Protein-Amino Acid	6%	
Electrolyte Mineral Water	7%	
Hormone	12%	
Pharmacology		14%
Nutrition - Normal and Dis.		8%
Genetics		5%
Growth and Development		5%
Cancer and Neoplasia		5%
Immunology and Allergy		5%
Transplantations		4%
Surgery Developmental Techniques		5%
Intra- and Extracorporeal Devices		2%
All Others		9%
Total		100%

Efforts are under way to determine the effectiveness of general outpatient research facilities. Also, the feasibility of funding of specialized technologies for general clinical research use is being explored. For example, a contract has been awarded to determine whether a minicomputer specifically designed for clinical research applications can be effectively used for a variety of clinical research data-handling needs. Centralized statistical data-handling capabilities may serve a variety of clinical research and clinical trials requirements. Another effort is under way to foster the development of special technologies, such as mass spectrometry for general clinical research use.

Research Highlights

Hypertension

The search continues for treatable causes of high blood pressure, which affects one in ten American adults and plays a significant role in the genesis of heart, kidney, and eye disease. Two new hormones have been discovered which cause the body to retain salt and which are present in greater amounts in some adult patients with hypertension. This suggests that a treatment designed to counteract the salt retention might provide a treatment for these patients. In addition, a new salt-retaining hormone has been dis-

covered to cause hypertension in some children, and a treatment which can lower the blood pressure has been developed.

A New Influenza Vaccine

The aim of current research is to develop improved vaccination materials against pandemic influenza. Current influenza vaccination uses killed influenza virus, which offers only incomplete protection. Using recently developed methods which can combine various strains of viruses, investigators at the NIH have combined an influence virus strain which does not grow at normal body temperature with an epidemic strain. The hybrid virus provokes a very mild respiratory infection, but provides substantial protection against the epidemic virus. During the past year, the hybrid virus vaccine has been administered to volunteers on a GCRC. The vaccine induced complete resistance to influenzal disease produced by challenge with virulent wild-type virus. Work is now being done to confirm the efficacy and safety of a newer live virus vaccine which may provide broad protection against recent virus mutations.

Bone Cancer

Physicians at a pediatric CRC have found a hormone treatment which significantly prolongs the lives of patients who are critically ill with osteogenic sarcoma. This condition is a highly malignant tumor which occurs in the rapidly growing bones of adolescents. By combining treatment with female hormones, which reverses certain metabolic disturbances characteristic of the disease, surgery to remove the primary tumor, and drug therapy to prevent its spread to other parts of the body, these investigators seemed to have arrested the progress of the disease in a majority of cases.

Thyroid Cancer

Patients with cancer of the thyroid gland have a much greater chance of survival when this disease is diagnosed at an early stage. A GCRC is currently refining a new diagnostic test with the capability of detecting this disease before the thyroid becomes sufficiently large to be recognized clinically. Investigators there have discovered that a protein of the thyroid gland, throglobulin, occurs in the blood in high concentration in patients with cancer of the thyroid, thus permitting early diagnosis. This unique diagnostic test may prove to be of considerable value in the early treatment and subsequent cure of this lethal disease.

Corneal Transplantation

Thousands of people who have become blind because of clouding or scarring of the cornea, a clear membrane which transmits lights through the front of the eye, can be very effectively treated with transplanted corneas taken from the dead. A technique has been developed by which corneas taken after death can be quick-frozen and preserved indefinitely, thus insuring a constant supply of this tissue for those who need it. In addition, studies of immunosuppressive therapy in patients receiving corneal transplants have led to

methods for longer-lasting, high-quality transplants.

Treatment of Kidney Disease

Advances in three different areas have resulted in an improved quality of life for patients with renal failure who must be treated with an artificial kidney or transplanted with a kidney from a diseased person. First, better dietary management has increased the period between necessary treatments with the artificial kidney. In addition, major advances have been made in the development of an artificial kidney which is wearable, thus enabling the patient to move about freely while being treated instead of being immobilized for several long periods of time each week. Finally, two changes have been made in the management of transplantation which much improve the chance of a successful regraft in the 45 percent of patients in which an initial transplant from a diseased individual has been unsuccessful. These are the continuation of immunosuppressive therapy up until the time of the failing first transplant, and the development of a kidney cell crossmatch which supplements the standard lymphocyte crossmatch. These modifications make it possible now to perform retransplantation of a cadaver kidney to patients with the same possibility of success as in first attempts.

Fiscal Status of the Program

The President's Budget for fiscal 1976 requested $41.6 million for the program and the final Appropriations Bill contained $42.6 million for the program. This compares with $42.4 million appropriated in fiscal 1972. Cost increases in the program have averaged almost 50 percent during this same period. In part, these cost increases have been offset by increasing use of type B service patients and doing some studies on an outpatient basis. However, this year it became necessary to award phase-out budgets to seven centers and to reduce all budgets by 6 percent below last year's level in order to achieve a balance between appropriations and expenditures. These fiscal stringencies will be somewhat relieved if the President's proposed budget for fiscal 1977 which requests $47.3 million for the program is appropriated.

Program Review

During the past year, the Program has been subject to review from a variety of distinguished commissions and panels. The President's Biomedical Research Panel recommended that the General Clinical Research Centers Program be reviewed with the intention of making it more widely available as a proper method of clinical trials for inpatients and outpatients and of paying proper Federal costs. The National Commission on Diabetes stated that clinical research can more effectively incorporate successful results of basic research through increased support for the existing General Clinical Research Centers. The Commission also recommended that the General Clinical Research Centers Program of the Division of Research Resources which supported 16 percent of the extramural diabetes research effort be awarded increases commensurate with its important role in diabetes research. In addition, the

Program has been extensively reviewed by an internal NIH Committee composed of senior representatives from each of the NIH extramural programs. This Committee has developed a position paper for the Deputy Director of NIH with recommendations on the role of the General Clinical Research Centers Program as it relates to the Institute's categorical centers and to other components of the extramural research program of NIH. The Committee has recommended a number of internal procedures to effect better coordination at NIH and also recommended that Institutes that receive center grants from more than one Bureau, Institute, or Division establish a local inter-institutional coordinating committee. Such a group might make cooperative efforts in the sharing of facilities and resources and the accomplishment of needed economies. Several other recommendations of this Committee are under consideration for implementation.

During the past year, the programs of the Division of Research Resources have been extensively evaluated by the Scientific Mission Study Panel. The Panel, commissioned by the Office of the Director, NIH, has been studying the effectiveness of the programs of the Division of Research Resources. A distinguished panel of specialists has examined extensive data relating to the Division's programs and made site visits to a variety of clinical research centers and other resources to gather information. The Panel is currently formulating its report and will be making recommendations to the Director of the Division of Research Resources and the Director, NIH, within the next few months.

Program Directors' Meeting

The GCRC Program Branch, in conjunction with the Program Directors, sponsored a one-day meeting in Atlantic City, the first such meeting in ten years. The meeting was designed to promote an exchange of information with staff and Program Directors with a view towards improving the program through better feedback and by promoting appropriate inter-center collaboration. Attendance was excellent and there was strong sentiment expressed that such meetings should occur on an annual basis. Dr. James Field, of Pittsburgh, and Dr. Charles Pak, of Southwestern Medical School, were elected as cochairmen to work with the program in planning an agenda for the next meeting and to develop a quarterly newsletter to provide for exchanging information and enhancing opportunities for collaboration.

Nurses and Dietitians

The nurses and dietitians have held several regional workshops during the past year in preparation for their biannual national meeting.

Mass Spectrometry

The General Clinical Research Centers Branch is seeking ways of making mass spectrometry (MS) technology available to clinical investigators on the centers. A letter has been widely distributed requesting statements of interest from MS facilities interested in launching trial collaborations

with clinical scientists. If there is enough interest, the Branch plans an RFP for a contract to initiate these research collaborations on a small scale.

Shared Core Laboratories

The GCRC Branch has begun working out the mechanisms of the shared core laboratory concept. This idea involves the sharing of sophisticated expertise, needed for clinical research but not widely available, between different laboratories in the program. Activities of the major core laboratories have been reviewed and those assay methods most suited to reciprocal exchange have been identified. At a recent meeting, GCRC Program Directors were given a general outline of the proposal which involves the support of enough additional resources to allow a core lab with experience in one kind of research methodology to supply it to another. No increase in funds is anticipated for this project, the new resources to be funded with savings from ancillary costs now expended in commercial laboratories. It is expected that an increase in knowledge exchange and collaborative research between centers will be an important benefit of the core laboratory sharing.

Clinical Associate Physician Program

This program was initiated three years ago to increase the number of highly qualified clinical investigators. During that time, nineteen positions have been funded which have provided time for researchers at a junior faculty level to pursue projects on CRCs. These physicians will not only augment their own level of investigational expertise, but serve as resource (both laboratory and clinical) for the CRC environment by interacting both, and under the direct supervision of senior investigators. The GCRC Branch is planning a review of this program within the next year to determine what beneficial effects it has had on the research community.

CLINFO

The CLINFO project (a collaborative contract between the GCRC Program and the Biotechnology Resources Program at the NIH and the Rand Corporation and their clinicians) is in its second of three years. Thus far, it has produced a prototype minicomputer system dedicated to the information processing needs of clinical investigators, and has installed this system at one of three evaluation sites. This investigational tool, which is aimed at facilitating the data storage, retrieval and analysis, has been favorably received by the research community. After the system is tested in two more Clinical Research Centers, a decision will be made to implement it in other CRCs as determined by scientific review.

Administrative Manual

The GCRC Program in collaboration with grantee institutions has prepared a 97-page Administrative Manual which established standardized procedures in the reporting of inpatient days and occupancies, and a single system for

documenting admittance, classification, furloughs and discharge of patients. The Manual provides information on the organization and administration of the centers, patient classification, physical facilities, application procedures, awards, expenditure reports, and hospitalization. Specifically, the Manual describes patient record systems with sample formats for fiscal records for each patient, monthly occupancy reports, and laboratory and X-ray charges. This Manual is currently in draft form and is proceeding through an administrative review and clearance by the Division of Research Resources and the Office of the Associate Director for Extramural Research and Training, OD, NIH, prior to printing and distribution.

Administrative Coordinators

The administrative coordinators of several regions have met during the past year. These individuals have assumed increasing responsibility for administration of the Clinical Research Centers and there are tentative plans to hold a national meeting to provide for informal discussions of problems to provide an opportunity for comparisons and to facilitate communication between centers and the GCRCPB.

Future Objectives and Plans

During the next year, several activities are planned. The role of the Clinical Research Centers in clinical trials will be examined with a view towards facilitating collaborative multicenter trials where appropriate. The role of outpatient clinical research will be evaluated. Computer systems as an aid to clinical research will be further tested with a view toward wider distribution on a competitive basis. Additional clinical associates will be added on a competitive basis as funds permit. An administration manual will be published and reporting requirements redesigned. Recommendations of the NIH-GCRC BID Clinical Coordinating Committee will be reviewed by NIH and appropriate implementing procedures developed in those accepted. The search for new technologies applicable to clinical research will continue. New centers will be funded in competition with the existing program as funds permit. Additional activities to promote communication between Program Directors, nurses, dietitians, and administrative coordinators will be undertaken.

Fiscal Year 1976
Annual Report
Biomedical Research Support Program
Division of Research Resources

The Biomedical Research Support Program was created during FY 1976 to administer the Biomedical Research Support Grant (BRSG) Program, formerly the General Research Support Grant (GRSG) and the Biomedical Sciences Support Grant (BSSG) Programs, and the recently established Biomedical Research Development Grant (BRDG) Program.

THE BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

The GRSG Program was authorized by Public Law 86-798 which was approved September 15, 1960, and the first awards were made in 1962. Recipients of the GRSG awards were health professional schools, hospitals, health departments and non-academic research institutions. In 1965, the companion BSSG Program was initiated. This program was conceptually identical to the GRSG Program, but provided funds to academic institutions other than health professional schools.

The President's budget for FY 1976 requested no funds for the GRSG/BSSG Programs. On January 28, 1976, the Congress overrode the President's veto of the FY 1976 HEW Appropriations Bill and restored $42,957,000 for the GRSG/BSSG Programs. The appropriation language for the Bill, House Report 94-311, page 45-46 and Senate Report 94-366, page 63-64 endorsed several program revisions concerning eligibility, allocation and usage of funds and support of small institutions. Those revisions were developed during the study requested by the Appropriations Subcommittees for Labor HEW of both Houses of Congress during the hearings on the FY 1975 budget and include:

- The merging of the General Research Support Grant (GRSG) and the Biomedical Sciences Support Grant (BSSG) into a single program, the Biomedical Research Support Grant (BRSG) Program, and the initiation of new administrative requirements. (See Eligibility, Computation of Awards, Administration of Grants and Site Visits).

- The establishment of the Biomedical Research Development Grant (BRDG) Program. Up to ten percent of the funds appropriated and apportioned each year for the BRSG Program was designated for support of the BRDG Program.

1. General Program Objectives

The general objective of the Biomedical Research Support Grant Program (BRSG) is to strengthen, to balance, and to stabilize Public Health Service supported biomedical and behavioral research programs. A distinguishing feature of the program is the opportunity it provides

grantee institutions to exercise on site-judgment regarding emphasis, specific direction, and content of activities supported, thus enabling the institution to respond quickly and effectively to emerging opportunities and unpredictable requirements, to enhance creativity, to encourage innovation, to provide for pilot studies, and to improve both physical and human research resources.

2. Eligibility

The same types of institutions formerly supported by the GRSG and BSSG Programs are eligible for the BRSG Program. Grantee institutions must have received at least $200,000 (including direct and indirect costs) in allowable Public Health Service biomedical and behavioral research grants for budget periods with beginning dates that fall within the latest complete Federal fiscal year. In addition, the degree of diversity, complexity, and breadth of the institution's total biomedical and behavioral research is considered in the review of applications. Previously eligibility for BSSG awards required $200,000 in NIH or NIMH research grants and $100,000 in such grants for GRSG awards.

3. Computation of Award

Awards are computed by application of the following formula to the allowable PHS biomedical and behavioral research project grants awarded to each applicant institution during the latest completed Federal fiscal year (entitlement) and adjusted by a uniform factor (prorated) to the funds available for the program. In prior years, GRSG and BSSG awards were calculated under separate formulas resulting in different ratios of entitlement to award for the two programs.

Revised Formula

Percentage Applied	Amount of Allowable PHS Biomedical & Behavioral Research Grant Support
15% of	the first $500,000 plus
10% of	$500,001 through $2,000,000
	plus
5% of	$2,000,001 through $6,000,001
0% of	$6,000,001 and over

The maximum credit permitted for any one allowable PHS biomedical or behavioral research grant to which the new formula can be applied is $500,000. This limit is a new policy in 1976.

4. Emphasis for Usage of Funds

Grants from this program support primarily those biomedical and behavioral research activities not readily or normally supported by PHS categorical research grant programs. Examples of such needs fall into two major categories: Project Support and Central Research Facilities.

Project Support

During the latest fiscal year for which reports are available, 8,008 projects were supported at an average level of $3,335 per project.

A. Pilot Research

- Explores new research ideas to test their validity and to provide preliminary findings necessary to support research project grant applications.

- Helps to assure higher quality, more promising, and often less costly research project proposals that eventually compete for support from other biomedical and behavioral research support programs.

B. Unforseen Requirements for Projects Supported from Other Sources, for Example:

- Repair or replacement of research equipment.

- Development by investigators of additional technical skills when dictated by interim research findings or the emergence of useful new techniques.

- Interim support of research personnel, equipment, and supplies to maintain research programs during temporary lapses in project grant support.

C. New Investigators

- Provides initial research support for new investigators and investigators newly relocated at an institution.

Central Research Facilities

- Provide to communities of investigators advanced costly and sophisticated instruments and equipment that cannot be justified by any single project.

- Provide research services and specialized expertise such as animal care, computer technology, and instrument design.

BRSG expenditures made in support of Projects and Central Research Facilities occur in the following categories.

Faculty	21.6%
Other Professional	7.4%
Other Personnel	24.0%
Equipment	24.1%
Supplies	14.3%
Other	8.6%

BRSG funds are used for purposes that do not require decision or approval by NIH staff and that are best decided by the grantee institutions with major savings on valuable time and overhead costs at both NIH and the grantee institutions.

Grantee institutions maintain and provide continuity to their entire research programs through the flexible use of BRSG funds. The major impact of the BRSG program is establishment of a stable research environment that provides maximal effectiveness and efficiency in the production of high quality biomedical and behavioral research with a minimum investment of BRSG funds. Consequently, the full scope of PHS supported biomedical and behavioral research is stabilized, balanced, and strengthened.

5. Administration of Grants

The following new requirements have been developed for grantee administration of BRSG funds.

- The grantee institution must name a program director who will be responsible for the institution's administration of the grant and for compliance with the policies and procedures of PHS and the grantee institution. This individual must be a scientist experienced in biomedical or behavioral research and administration.

- Each grantee must also establish intra-institutional mechanisms acceptable to the National Institutes of Health:

  - To assure broadly based review for advice on the use of the grant funds, with input from both scientific and administrative personnel of the grantee institution.

  - To disseminate information about the availability of the Biomedical Research Support Grant funds and the results achieved through use of the funds, and

  - To assure adequate programmatic and fiscal accountability.

Support of research salaries of tenured faculty is permitted only on a short-term basis provided it can be justified. Such support to any one person may not exceed a cumulative total of six months in any two consecutive grant years except with prior approval by the National Institutes of Health. In the event of institution-wide salary increases, the prior approval requirement will be waived for those increases in the salaries supported from PHS grants allowable in the computation of the BRSG award, but only until the continuation, renewal, or termination of those PHS grants, whichever occurs first.

Supplementation of ongoing funded PHS research project grants is permitted only for unexpected or emergency needs.

Alterations and renovations of research facilities may be charged to the grant not to exceed 20 percent of the BRSG award for the current year, or $40,000, whichever amount is smaller. Carryover of this authority may be allowed with justification for up to one year, subject to prior approval by the National Institutes of Health.

6. Site Visits

Each year site visits will be made to a sample of grantee institutions, representing all categories of institutions, and to any institution where NIH staff has identified a need for additional information concerning management of the grant and its accomplishments. Purposes for the visits include continuing assessment of program goals and policies, improvement in grantee management and correction of deficiencies, enhancement of program effectiveness, and confirmation of progress reports. This policy of site visits is new in 1976.

7. Program Data

The following tables describe how BRSG funds are used, and the amounts of funds available and their allocation to grantees.

TABLE I

FY 1974 Expenditure of Biomedical Research Support Grant Funds by Activity

	Number	Dollars (in thousands)	% of Total Dollars
RESEARCH PROJECTS	8,008		
New Pilot Proj.	2,024	4,874	12.4
Cont. Pilot Proj.	1,233	2,924	7.5
New Reg. Res. Proj.	1,835	6,539	16.7
Cont. Reg. Res. Proj.	2,916	12,368	31.5
CENTRAL RESOURCES			
Animal Facility		2,323	5.9
Computer Facility		706	1.8
General Use Equipment		2,203	5.6
Instrument Shop		339	.8
Central Lab Facility		2,138	5.5
Photog. and Med. Arts		230	.5
Other		1,790	4.6
RESEARCH TRAINING		1,748	4.5
OTHER ACTIVITIES		1,038	2.7
TOTAL		39,220	100.0

TABLE II

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM
(Dollars in Thousands)

Year	Funds Available for NIH Research Grants 1/	BRS Authorization Ceiling (15% of Funds Available for NIH Research Grants)	Funds Available BRS Program 2/ Amount	Percent of Funds Available for NIH Research Grants
1966	$ 604,377	$ 90,657	$45,200	7.5
1967	681,197	102,180	51,700	7.6
1968	727,366	109,105	59,700	8.2
1969	729,230	109,385	60,700	8.3
1970	744,061	111,609	57,677	7.8
1971	765,510	114,827	54,200	7.1
1972	901,119	135,168	55,212	6.1
1973	820,913 1/	123,137	60,700 2/	7.3
1974	1,091,795	163,769	45,149 3/	4.1
1975	1,142,782	171,417	42,957	3.7
1976	1,229,814	184,472	42,957	3.5

1/ Thru 1972 includes NIMH
2/ Includes 33.5 million impounded funds
3/ Excludes Minority Biomedical Support Program funds after 1973

TABLE III

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

Distribution of Biomedical Research Support Grants by Size of Awards
Fiscal Year 1976

Size of Grant (in thousands)	Number of Institutions
Under - $ 30.0	74
$ 30 - 49.9	87
50 - 99.9	116
100 - 149.9	60
150 - 199.9	48
200 - 249.9	19
250 - 299.9	37
TOTAL	441

Grant Range	Amount
Low	$ 15,658
High	261,305
Average	96,955

Entitlement* Compared to BRSG Funds Awarded

Fiscal Year	Entitlement *	BRSG Funds Awarded	Ratio (%) BRSG/Entitlement
1976	$995,465,535	$42,957,000	4.32

*Total allowable PHS grants used for computation of BRSG awards.

TABLE IV

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

Number of Grantees by Type for the Biomedical Research Support Grant Program FY 1969 - 1976

Type of Grantee Institution	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	Revised FY 1974	FY 1975	FY 1976
Medicine	99	100	100	101	104	104	107	106
Dentistry	49	49	33	34	34	33	34	26
Osteopathy	5	5	0	0	0	0	1	1
Pub. Health	12	12	12	12	12	12	12	12
Pharmacy	12	15	15	16	14	12	17	13
Vet. Med.	17	17	17	16	15	14	15	10
Nursing	0	0	2	4	3	4	5	3
Allied Health	0	0	0	0	1	1	1	0
Hospitals	75	79	76	79	71	66	71	63
Health Dept.	3	3	2	2	2	2	2	2
Res. Inst.	58	64	69	75	71	70	75	71
Other Academic[1/]	110	113	112	117	113	108	121	134
TOTAL	440	457	438	456	440	426	461	441

1/ Academic institutions other than health professional schools

THE BIOMEDICAL RESEARCH DEVELOPMENT GRANT PROGRAM

The appropriation of $42,957,000 for the BRSG Program in FY 1976, authorized the establishment of the proposed Biomedical Research Development Grant (BRDG) Program. The purpose of the BRDG Program is to increase the biomedical and behavioral research capacity of new, small, and developing health professional institutions which presently have a minimal research base but which offer potential to develop and sustain a high quality research program with a limited involvement of BRDG funds over a short period of time. Eligibility for the BRDG program would be limited to those health professional institutions which have received less than $200,000 in allowable Public Health Service (PHS) research grants in the latest complete Federal fiscal year. BRDG funds could be used to support recruitment of personnel, initial salary support of key investigators, central or shared research resources including equipment, facilities, support personnel, technical assistants and other programs and activities which are directly relevant to establishing and improving their biomedical and behavioral research capacity aimed at meeting their specific institutional goal. Up to ten percent of the funds appropriated and apportioned each year for the Biomedical Research Support Grant Program have been designated for support of the BRDG Program. Applications would be submitted for up to three years of support in amounts averaging up to $100,000 per year, i.e., a two-year award may not exceed $200,000; a three-year award may not exceed $300,000. With exceptional justification, awards may be renewable on a competitive basis, but support to one institution may not exceed a total of six years or $600,000.

The decision was made not to launch the BRDG Program in FY 1976. This decision was based on several concerns, one of which is the fact that the time required for announcement of the Program and receipt and review of application was insufficient to issue awards prior to the end of this fiscal year. The prime concern, however, relates to the commitment for continued support. The BRDG Program is to be one in which the development efforts of successfully competitive institutions would continue for a three-year period with an option to apply for a renewal for an additional three years of support. Since no funds were requested for the Biomedical Research Support Program in the President's budget for 1977, NIH was unable to make a "moral" commitment to sustain the support of such a developmental effort if it had been possible to launch the BRDG Program in 1976.

A decision was made to develop draft guidelines, to plan for announcement of the program, to charter a review committee and to hire needed personnel, in order to activate the BRDG Program if funds should be made available for the BRSG and BRDG Programs in 1977.

Fiscal Year 1976
Annual Report
Minority Biomedical Support Program
Division of Research Resources

A. Introduction

1. Historical

The Minority Biomedical Support (MBS) Program was deemed necessary in order that ethnic minorities may have equality of opportunity to participate in biomedical research. The Division of Research Resources launched this program in 1971 and made the first awards in June of 1972. Accordingly, the program is intended to encourage increased involvement of ethnic minority students and faculty in the biomedical sciences and in health professions so that the nation can benefit from this untapped resource.

2. Goals of the Program

The most important of all research resources are people. Minorities, a large segment of the talent in this country, have been an untapped resource for enhancing biomedical research. The NIH has elected to tap this resource through the MBS Program.

The program goals are: to increase the numbers of ethnic minority faculty and student investigators in the biomedical sciences and to broaden the opportunities for research and research participation by ethnic minorities. The MBS Program is the NIH's major effort in providing opportunities for minorities to participate in biomedical research. This is a recognition that minority biomedical investigators can make a significant contribution to furthering the mission of the NIH and should be provided that opportunity.

B. Program Highlights

The MBS Program is an entirely new program to the NIH and thus has been experimental and changing in nature. It is unique in that it is centered in institutions that generally have not been NIH grantees and have had minimal biomedical research involvement. It is also unique in that one of the main elements of the program is undergraduate research participation. Undergraduate students are intimately involved in biomedical research of participating faculty at the grantee institutions. The students contribute to all aspects of a project including publishing and presenting papers at scientific meetings.

1. The Xavier MBS Symposium

Xavier University in New Orleans, through their MBS grant, conducts an annual symposium where MBS participants present papers on their research. There has been a tremendous increase in the number

of participants attending and the number of papers presented since the first symposium was held in 1973. The following table indicates the growth:

TABLE I

	1973	1974	1975	1976
Numbers attending	250	470	900	1300
Papers presented	76	165	280	370

2. Cooperative Program with the National Heart and Lung and Blood Institute (NHLBI)

Efforts were expended in the later part of 1975 and the early part of 1976 which led to the funding of a significant number of MBS projects by NHLBI. While most of the projects funded by NHLBI were ongoing MBS projects, a few new projects, submitted as supplemental applications, were reviewed and submitted for their consideration.

The NHLBI agreed to provide for FY 76 a total of $526,358 (direct and indirect costs) to DRR/MBS for the purpose of supporting MBS/NHLBI relevant projects. The NHLBI divisional breakdown for MBS projects is as follows:

TABLE II

DRR/NHLBI Cooperative Program Support

	No. of Project	Direct Costs	Indirect Costs	Total
Division of Lung Diseases	4	77,727	17,190	94,917
Division of Heart and Vascular Diseases	16	241,713	19,125	260,838
Division of Blood Diseases and Blood Resources	5	147,838	22,765	170,603
Total	25	467,278	59,080	526,358

Funds received from NHLBI by DRR for MBS projects represents an increase from $113,696 in FY 1975 to $526,358 in FY 1976 or $412,662. NHLBI has agreed to underwrite the funding listed in Table II for the duration of the Grant Period of the parent grant.

A procedural set of guidelines has been developed by NHLBI and DRR jointly which will be used to handle NHLBI relevant projects included in future MBS applications. It is expected that these guidelines will be adopted as a model for developing the necessary logistics of interphasing the MBS Program with other BID's.

3. Cooperative Program with National Cancer Institute (NCI)

The 1975-1976 year has achieved an intensified cooperation between the MBS Program and the NCI. In August, 1975, NCI provided the MBS Program with one of their Expert Consultant slots, to take over the responsibility for coordinating the selection of Minority Biomedical Support projects with cancer relevance and submit them to the NCI. Further, a committee was formed within NCI to review those projects submitted from MBS to NCI relative to whether they are within the mission of NCI and to facilitate transfer of funds. The following table shows the extent of NCI support for MBS projects in FY 1976.

TABLE III

DRR/NCI Cooperative Program Support

Number of Projects	Direct Costs	Indirect Costs	Total
20	$541,190	$117,875	$659,065

Funds received from NCI by DRR to MBS projects represents an increase from $228,268 in FY 1975 to $659,065 in FY 1976 or $430,797. NCI has agreed to underwrite the funding listed in Table III for the duration of the grant period. A joint NCI/DRR Cooperative Minority Biomedical Support Program brochure is available for distribution emphasizing the cooperative effort and encouraging research participation by minority scientists in biomedical research relevant to the Cancer Institute.

4. Program Accomplishments

In June of 1975, 293 MBS student participants graduated from their respective institutions. About 76 percent (225) went on to advanced training. Of this total, 78 are presently enrolled in medical

schools, 13 in dental schools, 35 in other health related schools and 99 in graduate schools. The following table is a comparison of these numbers with those of June 1974.

TABLE IV

Career Choices of MBS Graduates

	June 1974	June 1975
Total MBS graduates	80	293
Number to medical schools	29	78
Number to dental schools	7	13
Number to other health related schools	10	35
Number to graduate schools	18	99
Total to advanced studies	64	225
Percent going on to advanced studies	80%	77%

About 410 different research projects were supported involving approximately 1,800 students and faculty. These investigators published 75 research papers and made 358 presentations at scientific meetings during the year ending June 1975. In the same period, 171 grant applications were submitted to various government and private agencies. Of those submitted, 96 were approved. Applications that had been previously approved yielded 116 grant awards during the same period for a total of $2.382 million dollars. These grants included 14 from NIH, 61 from other government agencies and 41 from non-government agencies. There are now four MBS investigators who have received Research Career Development Awards from NIH.

In the spring of 1976 at least ten MBS research papers will be published in a special supplement of the Federation Proceedings (Federation of American Societies for Experimental Biology).

C. Program Status

The MBS program presently supports 76 grants involving 82 institutions. Two of the grants involve more than one institution. The following table is an indication of the types of applications funded and the funds awarded.

TABLE V

MBS Awards FY 1976

Type	Number	Amount
New	4	385,631
Renewal	3	298,886
Supplemental	7	570,328
Continuation	69	7,545,578
Total awards	83*	8,795,423**

*Seven grants were supplements to the ongoing grants, therefore only seventy-six different grantees are involved.

**Includes $1,185,423 from NCI and NHLBI for support of individual projects in areas related to NCI and NHLBI.

Fiscal Year 1975 Annual Report
Office Grants and Contracts Management
Division of Research Resources

The Office of Grants and Contracts Management was established by the Director, DRR, on October 29, 1975. This office is designed to accomplish the following functions:

1. Collaborate with Program Directors in the formulation of Division and NIH policies and procedures relating to the management of the grant and contract program.

2. To interpret and apply policies and procedures relating to the business management of grants and contracts.

3. To provide administrative and financial review of grant applications and contract proposals and to collaborate with Program Directors in grants negotiation, award and administration.

4. To provide administrative and technical support in the development, execution, and monitoring of grants and contracts programs including budget forecasting.

5. To maintain liaison with grants and contracts management staffs in other Institutes, with central OD/NIH offices, and with grantees and contractors.

In other words, the Office of Grants and Contracts Management (OGCM) is a centralized office which provides coordinated grants and contracts management expertise for all DRR Programs.

The OGCM is designed to:

1. Lead to better or optimal utilization of all grants management professional and support staff.

2. Help to assure coordination of DRR programs.

3. Assist in developing a more flexible Division organizational structure.

4. Assure a broader opportunity for each individual working in grants management to function at his/her highest level of capacity.

5. To provide the administrative structure required to support and maintain a valid and effective focus for the administrative management of multi-categorical research resource grants.

Individual grants management staff are assigned to collaborate with Directors of each of the Programs so that their highly specialized training and knowledge remains available for the team approach to managing resources.

Since the establishment of OGCM in October, 1975, the primary staff assignments of grants management professionals and support personnel have not been changed. However, the staff of the office has been reduced by one position. A pilot training program was conducted, proven successful, and, on the basis of that successful pilot, additional professional development activities will occur so that grants management staff who have previously been exposed to one of the Division's programs will, during the course of the next several months, be exposed to other programs within the Division.

Currently, Grants Management and Program Branch staff are engaged in subjects of discussions regarding the assignments of particular responsibilities to the Office of Grants and Contracts Management and to the Program Branches. Coincident with the assignment of responsibilities, the decision has been reached on physically relocating the Grants Management staff into a centralized area. It is envisioned that a new location will provide both the continuing close working relationships between the organizations and will provide a new sense of team work among all the staff of the Office of Grants and Contracts Management.

Fiscal Year 1976 Annual Report
Office of Program Analysis
Division of Research Resources

The Office of Program Analysis is responsible for establishing and managing an appropriate Division-wide data base to support decision-making in the various program areas and at the level of the Office of the Director, DRR. The many interactions of the data system with the various grants management and scientific personnel to utilize data and information effectively in decisions, comprise the Division's concept of an Integrated Information Management System (IIMS). Fundamentally, this system's charge is to produce data, reports, records, graphics and statistics for purposes of planning, developing and assessing programs and for providing day-to-day mechanisms for monitoring grants and contracts operations.

During the past year, the office was renamed the Office of Program Analysis (formally known as Program Analysis Branch) and directed to a renewal of its plan for an IIMS. In this process, the office reviewed the prospectus of what it had planned to do in its 1974 version of an IIMS. Parts of that system, no longer currently of value, were discontinued. Examples of this were cessation of the publications, known as the DRR Handbook, and the DRR Data Publications. Other parts of the IIMS that remained undone have now been almost entirely implemented. Examples of this latter progress include redesign of report forms and initiation of data collection for research projects in the Laboratory Animal Sciences and Primate Research programs. This office also assisted the Biotechnology Resources and Biomedical Research Support programs in developing scientific classifications of the research projects being carried out through their resource support. OPA is now entering data on the scientific aspects, i.e., diseases, fields, disciplines, etc. for each. In the case of BRP, staff in OPA are performing the initial indexing according to the classification scheme.

Recently, utilizing these computer stored classifications and other captured data on the NIH grant support of investigators using the DRR centers, this office has produced program wide summations of the above data for the ARP, General Clinical Research Centers, and Minority Biomedical Support programs. These data have been valuable in relating DRR program emphases to the research interests of the other NIH components.

As part of its earlier effort in developing version I of the IIMS, another product was made available to the GCRC program this year. Generated by the computer and called the Budget worksheet, it aggregates data in a manner that (1) expedites the preparation of program budget, (2) permits some unique capabilities for program analysis, and saves clerical and grants management staff time.

Over a period of several council rounds, the OPA has been responding to some expressed needs for data for council. These efforts have progressed further this year resulting in a revised format for the data booklet, which summarizes the active grants, and displays the disposition (approved, awarded, etc.) of grants and contracts over the most recent council rounds.

The key innovation, occurring this year as a consequence of the OPA review of IIMS version I, was the conception and considerable advance into an improved system, version II of the IIMS. This was accomplished through an entirely new assessment of systems objectives. Based on decision techniques and selected concepts of the National Cancer Institute's Management Information System, and the National Heart and Lung Information System, the office has been able to develop an overall plan and strategy, and continues to work out the detail of systems' requirements.

The DRR IIMS version II is composed of several major subsystems of which the Office of Grants and Contracts Management (OGCM), budget and scientific program systems are receiving priority for development in that order. For the most part the OGCM has, therefore, received the greatest attention and is well advanced in concept and specific requirements at this time. It was evolved by carefully weighing the utility of data uniformly important to all grants managers across all DRR programs; these data were defined as those contained in a prescribed set of grant documents in common usage.

The basics of the subsystem consider the kinds of day-to-day decisions made, the criteria used to make decisions and the forms where the data involved with the criteria are found and compiled in the accounting processes. This subsystem has been described in a report, displaying all the data, their documentary and program source of origin, the nature of formats and sorts for output requirements of the data, and the numerical relationships of raw and summary data, i.e., direct costs plus indirect costs equals total approved budget costs. For this system OPA also assisted in the development of a special DRR Internal form for collecting contract information and another form for collecting grants management statistical estimates related to program funding.

This documentation now in revision will serve as a guide for systems design for computer processing, as documentation of data standards, and as a guide to grants managers for becoming familiar with Division programs other than their own. In an addendum to this documentation booklet, OPA has further identified select requirements for grants information on a program-by-program basis. These required data, such as occupancy rate, and number of minority graduates are specific, usually to only one program. Some of the less well known documentary sources for these, include the GCRC Report of Expenditures worksheet, and the MBS fact sheet.

Besides processing its customary large number of requests for DRR support of research in diverse fields of science, such as genetics, Cooley's anemia, arthritis, etc., the office has responded to a broad array of data requests. Most specifically, this year the office has provided data from its own system and DRG's Impac system to assist the contract studies being conducted on the scientific mission of the DRR, by Bolt, Beranek and Newman.

Fiscal Year 1976 Annual Report
Office of Science and Health Reports
Division of Research Resources

Prior to the start of the fiscal year, the Office had made arrangements for most of the July issue of the Federation of American Societies for Experimental Biology's Federation Proceedings to be devoted to the research activities of the Division-supported Primate Research Centers. The Information Officer and the Primate Center Chief coauthored the introductory article. Approximately a dozen papers by various scientists from individual primate centers appeared in the FP "Special Topic."

To highlight the publication, a press briefing was created, conceived, and carried out by the Office at the California Primate Research Center, Davis. It featured the health-related studies of three center scientists whose articles appeared in the Federation Proceedings. Included was the work of the center embryologist, who explained how the fetal period in pregnancy (end of the 1st trimester to birth) had been neglected in drug testing and how serious fetal problems could be caused by drugs the mother takes after the embryonic period ends. Through his work with a common drug that causes birth defects, he urged the testing of pharmaceuticals and other agents during the entire period of pregnancy.

Another scientist, working with animals, had uncovered the fact that "normal" lungs apparently adapt to photo chemical smog at average levels present in California's smoggiest area, the Los Angeles Air Basin. He discussed adaptation and how damage "disappears." He showed how the amount of further damage was apparently "concentration dependent" (on further high levels of ozone.)

A third scientist presented her work on marijuana use. Using non-human primates, she showed that a behavioral trait, "irritable aggressiveness," apparently appears and is directly related to the levels of this drug which build up in the body with frequent, long-term use.

The press briefing was attended by over 25 science writers, plus correspondents from the electronic media. Included were United Press International, Associated Press, Copley News Service, the Journal of the American Medical Association, the New York Times, the Los Angeles Times, the Daily Democrat, the Sacramento Union, the Davis Enterprise, National Public Radio, the San Francisco Chronicle, UCD Spectator, Physicians Radio Network, KGO-TV, KUVU-TV, KRON-TV, KOUR-TV, KRCA-TV, and KXTV.

During the science writer's morning briefing, each investigator gave a 20-minute presentation, followed by a question and answer session. At lunch time, correspondents had an opportunity to talk to each scientist personally. In the early afternoon, the Center Director gave a tour of the facility. While this was taking place, the press briefing for the electronic media began. Each scientist made a short 5-minute synopsis of their work for TV followed by a question and answer session with the reporters. The TV reporters then toured the outdoor cage area with the scientists.

A complete press kit, developed by the Office, was distributed. It carried background fact sheets, biographies and photographs, plus reprints of the three papers from the Federation Proceedings.

Hundreds of stories and pictures based on the press conference appeared in various media. The Journal of the American Medical Association ran a three-part series devoted to the papers. Bioscience ran an article. For the first time in the university's history, the Associated Press and the United Press International attended a function at the Davis campus and ran stories over their national wire.

Requests poured in from all over the world for reprints of the material in the Federation Proceedings. These copies were produced by the Office. Each primate center director received over 100 reprints for distribution to visiting scientists; the material was also widely distributed at NIH. As the year drew to a close, Plenum Press in New York was in the process of publishing the papers as the sixth in a series of FASEB monographs.

During the year, the Office also ran the Press Room at the 1976 Xavier-Minority Biomedical Support Symposium in New Orleans. Approximately 400 scientific papers were presented to the 1200 attendees at that meeting. The Office operated a press room for three full days, developed a press kit for visiting newsmen, and took many photographs for later use, including a full-page spread in the Louisiana Weekly. This spread will be reprinted by Xavier University and will be distributed widely at NIH and through MBS grantee schools.

An Office-written exclusive feature story from the Symposium was run over the Knight Newspaper Syndicate which includes 33 daily newspapers with over a 24 million circulation.

An advance release was written prior to the Xavier event and mailed to the minority press. A follow-up story went to specific minority presses, including Spanish publications, with an appropriate picture.

Office staffers made many radio tapes with Symposium participants. Four separate interviews were fed by phone to the Mutual Black Network in Washington which covers 94 stations throughout the country, and to the National Black Network in New York which has 74 participating stations. Also exclusive interviews were fed to National Public Radio and to the Voice of America. An interview went to the American Broadcasting Radio Network via New Orleans outlet WGSO.

Based on an Office-written feature, a major story on cancer test studies, presented at the MBS Symposium, appeared in the Los Angeles Times, by science writer Harry Nelson. It gave credit to the Division for support of the studies through MBS.

A portable light-weight exhibit was prepared by the Office and was displayed at the Symposium. It told the MBS story in words and pictures. It could be carried to the site and assembled in less than five minutes.

Earlier in the year, an Office-prepared backgrounder plus a picture became the source of a Minority Biomedical Support article in the September issue of Bioscience. The article credited the Division for support of the MBS program and quoted the Acting Director of MBS as predicting: "there will be 1200 more budding biomedical scientists coming up from this group alone."

In addition, the Office drafted a letter to the editor for the DRR Director's signature commenting on an article that discussed "underrepresentation of the minorities in the biomedical sciences," yet failed to recognize the existence of the MBS program. That letter was published in the October issue of Bioscience.

During the year, the Office furnished background information and pictures on primate research centers to Oasis, published by the Social Security Administration. This publication did a major piece on the program in its nationally-distributed journal.

An Office-generated story and picture on the first primate infant produced through embryo transfer, which took place at the Southwest Foundation in San Antonio, received wide play at mid-year. U.S. Medicine, Science News, NSMR Bulletin, and the Journal of the American Veterinary Medical Association carried it. The Associated Press National wire, and the Chicago Daily News Service ran the story with a credit for Division support. News and Features from NIH and the NIH Record also carried the story.

In the audiovisual arena, the Office continued to produce numerous slides for the Division's various interfacing and other presentation activities. The slides were carefully designed to convey maximum information about DRR programs. In addition, the Office produced color prints of the various slides for presentors and viewers.

During the year, the Office handled approximately 15 Freedom of Information requests involving over 40 grants. It coordinated requests with several other NIH components, including the National Cancer Institute.

Requests for Division booklets continued to be strong, with the majority of requestors interested in our clinical research center booklets: "Research Advances in Human Transplantation," and "How Children Grow." Over 17,105 publications were distributed by the Office during the fiscal year. They were mailed as a result of 3,843 individual requests. Bulk requests included a whopping 7,000 copies of Division booklets for distribution at the NIH Visitor's Center and at the NIH Open House.

Among other significant placements made about DRR program activities during the year were : in U.S. Medicine and the New York Daily News on an indepth Office-written report about Dr. Donald A. Glaser's Mass Cellular Laboratory at the University of California at Berkley; in International Wildlife on an interview with Dr. Charles McPherson about the primate supply situation; in the New York Times on the official dedication of Dr. Oleg Jardetsky's NMR facility at Stanford University; and in Medical Group News on the Reconstituted Cell Technique made possible by use of the million-volt electron microscope at the University of Colorado.

The Office has arranged for the publication of ten scientific papers developed by participants of the MBS program in a future issue of Federation Proceedings, with an introductory article coauthored by the Information Officer and the Acting Director of the Minority Biomedical Support Program.

The photography activities of the Office were accelerated during the year with major assignments in covering the Xavier-MBS Biomedical Symposium in New Orleans, the DRR Workshop at Harper's Ferry, the U.S. Savings Bond Campaign, and numerous other program-support photo requests.

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